AMERICAN CHEMISTRY COUNCIL'S

LRI Annual Science Meeting

June 24–25, 2003
Hyatt Dulles
Herndon, Virginia
Welcome

On behalf of the American Chemistry Council’s (ACC) Strategic Science Team (SST) we would like to welcome you to the first Annual Science Meeting of the ACC’s Long-Range Research Initiative (LRI). Through the LRI, the chemical industry sponsors independent research to expand scientific knowledge of the potential impacts that chemicals may have on the health of human and wildlife populations and the environment. Each year the LRI will hold a meeting to highlight the research projects underway and to focus on a significant, overarching research issue. This 2003 LRI Science Meeting explores the future of exposure research.

The LRI sponsors research of highest priority to society, as well as to the chemical industry. The LRI expands the industry’s commitment to Responsible Care®, the chemical industry’s global initiative to improve the environment, health and safety.

LRI sponsors research based on highest scientific merit and relevance to the program’s mission and objectives. The LRI is sponsoring projects at leading research institutes, government agencies, academic institutes, and research organizations. For example, the CIIT Centers for Health Research (CIIT) conducts research in the areas of its expertise, specifically mechanistic research to advance the science used to address public health issues. All the research is performed independently. Although the proposed work is reviewed for high scientific merit by external scientists and for relevance by industry scientists, the investigators are responsible for experimental design, selection of chemicals, conduct of the work, and publication of the results in peer-reviewed scientific journals. All the results are made public, without approval of the LRI.
The International Council of Chemical Associations (ICCA) provides global coordination for its member associations sponsoring research into basic questions about the health and environmental impacts of chemicals. ACC, the European Chemical Industry Council (Cefic) and the Japan Chemical Industry Association (JCIA), through the ICCA, have coordinated research projects and research strategies in key areas. The LRI involves industry and non-industry scientists from all over the world.

We hope this meeting will provide a forum for you to meet many of the scientists and learn more about LRI projects underway.

Carol J. Henry, Ph.D., D.A.B.T.  James S. Bus, Ph.D., D.A.B.T.  
ACC Vice President, Science and Research  Dow Chemical Company  
Co-Leader, LRI Strategic Science Team  Co-Leader, LRI Strategic Science Team

Organizing Committee Members

Dr. Tina Bahadori, American Chemistry Council  
Dr. Jim Bus, Dow Chemical  
Dr. Judy Graham, American Chemistry Council  
Dr. Raymond Loehr, University of Texas  
Ms. Cheryl Morton, American Chemistry Council  
Dr. Robert Rickard, DuPont  
Dr. Zachary Wong, ChevronTexaco

The American Chemistry Council represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people’s lives better, healthier and safer. The business of chemistry is a $460 billion enterprise and a key element of the nation’s economy. It is the nation’s largest exporter, accounting for ten cents out of every dollar in U.S. exports. Chemistry companies invest more in research and development than any other business sector. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation’s critical infrastructure.
Meeting Highlights

Keynote Speeches

<table>
<thead>
<tr>
<th>Day I</th>
<th>Day II</th>
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<tr>
<td><strong>Exposure Analysis: An Integral Part of Disease Prevention</strong></td>
<td><strong>EPA’s Programs on Use and Application of Exposure in Risk Assessment and Management</strong></td>
</tr>
<tr>
<td>Dr. Samuel Wilson</td>
<td>Dr. Paul Gilman</td>
</tr>
<tr>
<td>Deputy Director</td>
<td>Assistant Administrator</td>
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<tr>
<td>National Institute of Environmental Health Sciences</td>
<td>Office of Research and Development</td>
</tr>
<tr>
<td>National Institutes of Health</td>
<td>U.S. Environmental Protection Agency</td>
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<tr>
<td>Health and Human Services (HHS)</td>
<td>(US EPA)</td>
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<tr>
<td>Deputy Director</td>
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<tr>
<td>National Toxicology Program</td>
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</tbody>
</table>

LRI Research Showcases
Six LRI-research projects underway will be highlighted with presentations delivered by the scientists leading the research.

Poster Sessions
Over 45 principal investigators are presenting posters describing their LRI-funded research. Viewing times when the authors will be present at their posters are Tuesday 1:00-2:30 PM and 5:30-7:00 PM. The posters may also be viewed during breaks and meals on Tuesday and during breakfast on Wednesday.

Plenary Discussion – Current National Exposure Research Activities
Six esteemed scientists will make presentations on exposure research, from source to fate, including field studies, modeling, biomarkers, dose, and the application of exposure research to health studies.

Panel Discussion – Envisioning the Future of Exposure Research
As a follow-on to the Plenary Discussion, nine experts will discuss future directions of exposure research with the objective of identifying topics of highest priority.
### LRI Focus Areas

Three **focus areas** were developed to frame the research strategy for the LRI and to stimulate and encourage strategic, multidisciplinary approaches to sponsoring research of highest quality and relevance to the chemical industry.

**Improved Methods**: Building the scientific foundation to evaluate the potential risks of chemicals to public health and the environment
- Human health and ecological effects screening and testing methods
  - Toxicity test methods emphasizing development
  - Integration and implications of new and emerging approaches in health effects research
  - Methods to detect effects on wildlife
- Human exposure methods
  - Methods for characterizing and estimating exposures
  - Interpreting and using biomonitoring data
- Interspecies, intraspecies, and target organ determinants of dose-response
  - Prediction of target tissue dose
  - Understanding toxicodynamics
  - Health hazard assessment methodologies

**Susceptibility Factors**: Identifying vulnerable groups (including children) and characterizing factors that may place them at higher risk
- Human health sensitivity factors
- Human exposure factors

**Chemicals in the Environment**: Understanding how they move and change along pathways from sources to humans and wildlife
- Human exposure assessment and analysis
- Ecosystem exposure analysis

Several issues cross-cut the focus areas, especially those related to children’s health and exposure.

For **children’s health**, the improved methods focus area seeks to develop better health test methods for the developing organism and the susceptibility factors focus area will characterize factors that make children more vulnerable so that health effect and exposure models will be more accurate.

**Exposure science** will be advanced by the (1) improved methods focus area as more cost-effective methods to measure exposure are developed, (2) susceptibility factors focus area as factors leading to higher-than-usual exposures (and hence risk) are identified, and (3) chemicals in the environment focus area as exposure measurements are incorporated into the exposure and verification of model development.
## Agenda

### Day I - Tuesday, June 24, 2003

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
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</thead>
<tbody>
<tr>
<td>8:00 AM – 12:00 PM</td>
<td>Registration</td>
<td>Prefunction area</td>
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<tr>
<td>8:00 AM – 9:00 AM</td>
<td>Continental Breakfast</td>
<td>Atrium</td>
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<tr>
<td>9:00 AM – 9:45 AM</td>
<td>Long-Range Research Initiative: Staying Ahead of the Curve</td>
<td>Concorde Ballroom B,C,D</td>
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<tr>
<td></td>
<td>Chair: Judy Graham (ACC)</td>
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<tr>
<td></td>
<td>• Welcome – Greg Lebedev (President and CEO, American Chemistry Council (ACC))</td>
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<td></td>
<td>• Overview: Long-Range Research Initiative (LRI) – Carol Henry (ACC)</td>
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<td></td>
<td>• LRI Research Programs and Projects – Jim Bus (Dow Chemical)</td>
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<tr>
<td>9:45 AM – 10:45 AM</td>
<td>LRI Research Showcase I</td>
<td>Concorde Ballroom B,C,D</td>
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<td></td>
<td>• Systems Biology and Dose-Response Assessment – Mel Andersen (CIIT Centers for Health Research (CIIT))</td>
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<td></td>
<td>• Formaldehyde and Chloroform: Rodents Cancers, Human Risks – Rory Conolly (CIIT)</td>
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<td>• Improving Risk Assessment of Contaminated Sediments: Accounting for Speciation, Multiple Routes of Exposure, and Complex Mixtures – James Shine (Harvard)</td>
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<tr>
<td>10:45 AM – 11:15 AM</td>
<td>Break</td>
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<tr>
<td>11:15 AM – 12:00 PM</td>
<td>“Exposure Analysis: An Integral Part of Disease Prevention”</td>
<td>Concorde Ballroom B,C,D</td>
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<td></td>
<td>Keynote Speaker: Samuel Wilson (National Institute of Environmental Health Sciences)</td>
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<tr>
<td>12:00 PM – 12:05 PM</td>
<td>Organization of Poster Sessions</td>
<td>Concorde Ballroom B,C,D</td>
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<td></td>
<td>Cheryl Morton (ACC)</td>
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<tr>
<td>12:05 PM – 1:00 PM</td>
<td>Lunch</td>
<td>Atrium</td>
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<tr>
<td>1:00 PM – 2:30 PM</td>
<td>Poster Session I</td>
<td>Concorde Ballroom A &amp; Aviator Suites</td>
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<td></td>
<td>Dessert &amp; coffee will be served.</td>
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</table>
### Plenary Session: Current National Exposure Research Activities

**Chair:** Tina Bahadori (ACC)
**Rapateur:** Debbie Bennett (Harvard)

- *Exposure Research: The LRI Perspective* – Tina Bahadori (ACC)
- *Persistence, Proximity, and Mobility: Tracking Human Exposure to Multimedia Pollutants* – Tom McKone (UC Berkeley)
- *EPA’s Human Exposure Measurement Program* – Linda Sheldon (US EPA)
- *Modeling Inhalation and Multimedia Multipathway Human Exposures to Environmental Pollutants* – Halûk Özkaynak (US EPA)
- *Role of Biomonitoring in Human Exposure Assessment* – Larry Needham (Centers for Disease Control (CDC))
- *Dose to the Target: The Critical Linkage between Human Exposure and Response* – Fred Miller (CIIT)

**Q & A (20 minutes)**

### Poster Session II

**Reception**

**Dinner**

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**Day I - Tuesday, June 24, 2003 (continued)**
## Agenda (Continued)

### Day II - Wednesday, June 25, 2003

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Location</th>
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<tbody>
<tr>
<td>8:00 AM – 9:00 AM</td>
<td>Continental Breakfast and Poster Viewing</td>
<td>Concorde Ballroom A &amp; Aviator Suites</td>
</tr>
<tr>
<td>9:00 AM – 9:30 AM</td>
<td>&quot;EPA’s Programs on Use and Application of Exposure in Risk Assessment and Risk Management&quot;</td>
<td>Concorde Ballroom B,C,D</td>
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<td></td>
<td>Keynote Speaker: Paul Gilman (US EPA)</td>
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<td></td>
<td>Chair: Zach Wong (ChevronTexaco)</td>
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<tr>
<td>9:30 AM – 10:30 AM</td>
<td><strong>LRI Research Showcase II</strong></td>
<td>Concorde Ballroom B,C,D</td>
</tr>
<tr>
<td></td>
<td>• Effects of Interindividual Differences in Human Nasal Anatomy on Upper Respiratory Tract Airflow and Inhaled Gas Uptake – Julie Kimbell (CIIT)</td>
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<td></td>
<td>• Improving the Foundation of Risk Assessment of Endocrine-Active Mixtures – Grantley Charles (Dow Chemical)</td>
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<td></td>
<td>• Development and Verification of Field-deployable Methods for Evaluating Exposure and Effects of Endocrine Active Substances in Wild Bird Populations – Larry Brewer (Springborn Smithers Laboratories)</td>
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<tr>
<td>10:30 AM - 10:45 AM</td>
<td>Break</td>
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<tr>
<td>10:45 AM –12:15 PM</td>
<td><strong>Panel Discussion: Envisioning the Future of Exposure Research</strong></td>
<td>Concorde Ballroom B,C,D</td>
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<td></td>
<td>Chair: Tina Bahadori (ACC)</td>
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<td>Rapateur: Debbie Bennett (Harvard)</td>
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<td></td>
<td>• Matti Jantunen (KTL-Environmental Health, Finland)</td>
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<td></td>
<td>• Mary Kay O’Rourke (U of Arizona)</td>
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<td>• Chris Saint (US EPA)</td>
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<td></td>
<td>• Germaine Buck (National Institute of Child Health and Human Development (NICHD))</td>
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<td></td>
<td>• Tom McKone (UC Berkeley)</td>
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<td>• Linda Sheldon (US EPA)</td>
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<td>• Halûk Özkaynak (US EPA)</td>
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<td>• Larry Needham (CDC)</td>
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<td></td>
<td>• Fred Miller (CIIT)</td>
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<tr>
<td>12:15 PM – 12:30 PM</td>
<td><strong>Closing Remarks</strong></td>
<td>Concorde Ballroom B,C,D</td>
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<td></td>
<td>• Jim Bus (Dow Chemical)</td>
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<td></td>
<td>• Carol Henry (ACC)</td>
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</table>
Scientists will be presenting their LRI-funded research projects during two poster sessions on Tuesday. Viewing times when authors will be present at their posters during these sessions are as follows:

<table>
<thead>
<tr>
<th></th>
<th>Poster Session I</th>
<th>Poster Session II</th>
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<tbody>
<tr>
<td>Odd-numbered posters</td>
<td>1:00-1:45 PM</td>
<td>6:15-7:30 PM</td>
</tr>
<tr>
<td>Even-numbered posters</td>
<td>1:45-2:30 PM</td>
<td>5:30-6:15 PM</td>
</tr>
</tbody>
</table>

The posters may also be viewed during breaks and meals on Tuesday and during breakfast on Wednesday. A map indicating the location of the posters by poster number is presented on page 13.

**LRI Research Project Posters**

**Improved Methods: Toxicity Test Methods Emphasizing Development**

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Authors</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Developmental Immunotoxicity of Dexamethasone in the Rat: Comparison of Fetal vs. Adult Exposure</td>
<td>R.R. Dietert and J. Lee</td>
<td>Cornell University</td>
</tr>
<tr>
<td>2</td>
<td>Pathologic and Immunologic Responses in the Respiratory Tract of A/J Mice After Intranasal Sensitization and Challenge with Trimellitic Anhydride</td>
<td>A. Farraj, J.R. Harkema, and N.E. Kaminski</td>
<td>Michigan State University</td>
</tr>
<tr>
<td>3</td>
<td>Can Non-Invasive Plethysmography Predict Respiratory Allergy to Chemicals?</td>
<td>S. Sigaud and L. Kobzik</td>
<td>Harvard University</td>
</tr>
<tr>
<td>4</td>
<td>Determination of the Potential Susceptibility of the Developing Immune System of the Rat to Immunosuppression by the Pesticide Heptachlor</td>
<td>R.J. Smialowicz, W.C. Williams, C.B. Copeland, and R.A. Matulka</td>
<td>National Health and Environmental Effects Research Laboratory (USEPA) and University of North Carolina at Chapel Hill</td>
</tr>
<tr>
<td>5</td>
<td>Cellular and Molecular Targets during Androgen-Mediated Male Reproductive Tract Development</td>
<td>C. Thompson, S.M. Ross, and K.W. Gaido</td>
<td>CIIT Centers for Health Research</td>
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</table>

**Improved Methods: Integration and Implications of New and Emerging Approaches in Health Effects Research**

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<tr>
<th></th>
<th>Title</th>
<th>Authors</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Designs and Strategy for Tests of Gene Environment Interaction</td>
<td>X. Liu, W.L. Kao, Y. Yao, T.H Beaty, and M.D. Fallin</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>8</td>
<td>The National Environmental Respiratory Center: Disentangling the Health Effects of Complex Mixtures of Air Contaminants</td>
<td>J. Mauderly</td>
<td>Lovelace Respiratory Research Institute</td>
</tr>
<tr>
<td>9</td>
<td>Toxicogenomic Approaches to Particle-Induced Lung Disease</td>
<td>O. Moss, E. Bermudez, and J. Everitt</td>
<td>CIIT Centers for Health Research</td>
</tr>
</tbody>
</table>
## Poster Sessions

### LRI Research Project Posters

### Improved Methods: Methods to Detect Effects on Wildlife

<table>
<thead>
<tr>
<th></th>
<th>Title</th>
<th>Authors</th>
<th>Affiliations</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>Evaluating Habitat Use to Improve Exposure Assessment in Ecological Risk Assessments</td>
<td>L. Kaputska</td>
<td>Ecological Planning and Toxicology</td>
</tr>
<tr>
<td>13</td>
<td>Effects of a Synthetic Estrogen on Aquatic Populations: A Whole Ecosystem Study</td>
<td>K. Kidd, C. Podemski, A. Salki, M. Paterson, D. Findlay, B. Park, and K. Liber</td>
<td>Freshwater Institute and University of Saskatchewan</td>
</tr>
<tr>
<td>14</td>
<td>EXPECT: Extrapolation Practice for Ecological Effect characterization of chemicals</td>
<td>K. Solomon</td>
<td>University of Guelph</td>
</tr>
<tr>
<td>15</td>
<td>Evaluation of Fence Lizard Eggs as a Reptile-Egg Screening Assay for Endocrine Disrupting Chemicals</td>
<td>L.G. Talent and D.M. Janz</td>
<td>Oklahoma State University</td>
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### Improved Methods: Methods for Characterizing and Estimating Exposures

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<thead>
<tr>
<th></th>
<th>Title</th>
<th>Authors</th>
<th>Affiliations</th>
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</thead>
<tbody>
<tr>
<td>16</td>
<td>A Comprehensive Chemical Exposure Framework Based on a Nested Loop Approach and a Taxonomy of Longitudinal Change in Exposure Related Parameters</td>
<td>P.S. Price, C.F. Chaisson, M. Koontz, C. Wilkes, B. Ryan, D. Macintosh, and P. Georgopoulos</td>
<td>The LifeLine Group Inc., GEOMET Technologies, Inc., Wilkes Technologies, LLC, Emory University, EHE, and Environmental and Occupational Health Science Institute</td>
</tr>
<tr>
<td>17</td>
<td>Design of a Comprehensive Chemical Exposure Framework</td>
<td>G. Whelan, M.A. Pelton, K.J. Castleton, M.S. Peffers, D.A. Tolle, and J.W. Buck</td>
<td>Battelle Memorial Institute</td>
</tr>
<tr>
<td>18</td>
<td>Developing PBPK Models for Testosterone Dosimetry in the Perinatal Period in the Rat and Systems Biology Approaches to EAC Risk Assessment</td>
<td>M. Andersen</td>
<td>CIIT Centers for Health Research</td>
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### Improved Methods: Prediction of Target Tissue Dose

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<th>Title</th>
<th>Authors</th>
<th>Affiliations</th>
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</thead>
<tbody>
<tr>
<td>19</td>
<td>Compound-Independent Dosimetry of Inhaled Material</td>
<td>B. Asgharian, J.S. Kimbell, B.A. Wong, and O.R. Moss</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>20</td>
<td>Transplacental Transfer of Genistein and Conjugated Metabolites in Sprague-Dawley Rats</td>
<td>S.J. Borghoff, C. C. Williams, H. D. Parkinson, and M. Sochaski</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>21</td>
<td>Olfactory Toxicity of Hydrogen Sulfide</td>
<td>Dorman, D.</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>22</td>
<td>Mechanisms of Olfactory Transport of Inhaled Metals</td>
<td>Dorman, D.</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>23</td>
<td>Mechanisms of Adaptive and Adverse Responses in the Respiratory Tract Following Low-Level Exposure to Inhaled Reactive Gases: Dosimetry Modeling Core</td>
<td>J. Kimbell</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>Poster Session</td>
<td>Title</td>
<td>Authors</td>
<td>Affiliations</td>
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<tr>
<td>24</td>
<td>Modeling Inter-individual Variation in Physiological Factors Used in PBPK Models of Humans</td>
<td>P.S. Price, R.B. Conolly, C.F. Chaisson, and J.S. Young</td>
<td>LINEA, Inc., CIIT Centers for Health Research, and Hebrew University of Jerusalem Institute of Earth Sciences</td>
</tr>
<tr>
<td>25</td>
<td>The Influence of Serum Binding Proteins and Clearance on the Comparative Receptor Binding Potency of Endocrine Active Compounds</td>
<td>J.G. Teeguarden and H.A. Barton</td>
<td>Environ International and National Health and Environmental Effects Research Laboratory (USEPA)</td>
</tr>
<tr>
<td>26</td>
<td>Cellular and Molecular Targets during Androgen-Mediated Male Reproductive Tract Development</td>
<td>C.J. Thompson, S.M. Ross, and K.W. Gaido</td>
<td>CIIT Centers for Health Research</td>
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<td></td>
<td><strong>Improved Methods: Understanding Toxicodynamics</strong></td>
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<tr>
<td>28</td>
<td>Dose Response for Androgen-Receptor-Mediated Gene Expression</td>
<td>R.B. Conolly, M. Andersen, and K. Gaido</td>
<td>CIIT Centers for Health Research</td>
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<tr>
<td>29</td>
<td>Cumulative Risk of Organophosphate Pesticides</td>
<td>Conolly, R.</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>32</td>
<td>Physiologically Based Pharmacokinetic Modeling of Genistein in Rats</td>
<td>P.M. Schlosser, S.J. Borghoff, N.G. Coldham, H.T. Tran, and M.G. Zager</td>
<td>CIIT Centers for Health Research, Veterinary Laboratories Agency (UK), and Center for Research in Scientific Computation</td>
</tr>
<tr>
<td>34</td>
<td>Chlorine Risk and Value-of-Information Analysis</td>
<td>A.M. Jarabek, M.E. Andersen, J.S. Kimbell, and P.M. Schlosser</td>
<td>National Center for Environmental Assessment and CIIT Centers for Health Research</td>
</tr>
<tr>
<td>35</td>
<td>Cell Proliferation and Apoptosis in the Developing Male Reproductive Tract</td>
<td>E. Kleymenova and K. Gaido</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>36</td>
<td>Species Differences in Biological Parameters and their Role in Extrapolating Biologically Based Carcinogenesis Models from Animals to Humans</td>
<td>L.R. Rhomberg</td>
<td>Gradient Corporation</td>
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### Poster Sessions

#### LRI Research Project Posters

<table>
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<tr>
<th>Poster Number</th>
<th>Title</th>
<th>Authors</th>
<th>Institution</th>
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<tbody>
<tr>
<td>37</td>
<td>Computational Modeling of Chloroform Cytolethality and Regenerative Proliferation</td>
<td>Y. Tan and R.B. Conolly</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>38</td>
<td>Role of Steroid Ligand Transformation in Chemical-Caused Alterations of Endocrine Functions</td>
<td>L. You</td>
<td>CIIT Centers for Health Research</td>
</tr>
<tr>
<td>39</td>
<td>Impact of Phytoestrogens on Susceptibility to Synthetic Endocrine-Active Compounds</td>
<td>L. You</td>
<td>CIIT Centers for Health Research</td>
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#### Improved Methods: Health Hazard Assessment Methodologies

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#### Chemicals in the Environment: Human Exposure Assessment and Analysis

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Dr. Judy Graham, American Chemistry Council  
Chair  
Dr. Graham serves as a Senior Director/Senior Scientist of the Long-Range Research Initiative (LRI) Team. Prior to joining the Council, she was with the U.S. Environmental Protection Agency’s Office of Research and Development for 32 years. During that time, she served as an investigator, a Principal Investigator, Chief of the Branch that conducts animal inhalation toxicology research, Deputy Director of the Health Effects Research Laboratory, Associate Director of the Environmental Criteria and Assessment Office—Research Triangle Park, and Associate Director for Health of the National Exposure Research Laboratory. She is a Fellow in General Toxicology of the Academy of Toxicological Sciences and is the elected President of the Board of Directors. She is a member of the Committee of Toxicology of the National Research Council and a member of the Federal Advisory Committee for the National Child Study. She has been elected President of the International Society for Exposure Analysis (ISEA), President of the Inhalation Specialty Section of the Society of Toxicology (SOT), and President of the Risk Assessment Specialty Section of SOT. Dr. Graham is an author of over 135 journal articles, book chapters, and conference proceedings (primarily on the health effects and health risks of air pollutants). She has a Ph.D. in physiology and pharmacology from Duke University.

Mr. Gregory Lebedev, American Chemistry Council  
Welcome  
Greg Lebedev was appointed President and Chief Executive Officer of the American Chemistry Council (ACC) on October 1, 2002. The ACC represents the interests of the $1.7 trillion dollar global chemical and plastics industry in the media, before the courts, and to governmental bodies in the United States and throughout the world. The business of chemistry is America’s second largest manufacturing industry and the largest exporting sector in the United States.

Prior to joining the Council, Mr. Lebedev served as Chief Operating Officer and Executive Vice President for International Policy and National Security Affairs of the United States Chamber of Commerce. In addition to running the day-to-day operations of the world’s largest business federation, he was Managing Director of the National Chamber Foundation, the public policy think tank affiliated with the U.S. Chamber, and the President of the Center for Corporate Citizenship, a philanthropic and governance resource of the business community.

From 1993 to 1997, Mr. Lebedev was Senior Vice President for Management and Finance of the American Trucking Associations (ATA), the trade federation representing the quarter trillion dollar U.S. trucking industry. He also served as Managing Director of the ATA Foundation, the policy research arm of the trucking industry. Additionally, Mr. Lebedev was a member of ATA’s Management Committee, and from mid-1997 until moving to the U.S. Chamber, he was ATA’s Acting President and CEO.

Prior to joining ATA, Mr. Lebedev served as Senior Vice President of IPAC, a Washington-based international consulting firm, where he directed projects associated with the reconstruction of Kuwait following the Gulf War.

Until 1990, Mr. Lebedev was a Senior Partner of the Hay Group, then one of the largest management consulting firms in the world and the flagship of Saatchi & Saatchi’s global professional services organization. In that capacity, he was a member of Hay’s U.S. Executive Committee, and directed all government, business, and international sector consulting activities of Hay Management Consultants/Washington, Syllogistics, Inc. and Hay Systems, Inc.
Mr. Lebedev also has considerable governmental experience, having been appointed by President Gerald Ford to the State Department post of Assistant Inspector General of Foreign Assistance/Deputy Assistant Secretary of State, where he directed policy and management evaluations of U.S. economic and military assistance programs abroad. For his leadership, Mr. Lebedev received the Department’s Superior Honor Award. Immediately before that assignment, he served in the Bureau for Security and Consular Affairs and was one of the youngest Deputy Assistant Secretaries in Henry Kissinger’s State Department. Mr. Lebedev was also a member of the White House Staff, where he was Deputy Special Assistant to the President, prior to his State Department tour.

Mr. Lebedev earned a Juris Doctor degree from the School of Law of the University of South Dakota; and he holds a Bachelor of Arts degree from the same university.

Mr. Lebedev is admitted to practice law before the United States Supreme Court and the District of Columbia bar. He was appointed by Secretary of Defense Dick Cheney to the Defense Advisory Committee on Women in the Armed Services in 1993. He serves on the board of directors of the National Chamber Foundation, the Center for International Private Enterprise (CIPE), and the American Society of Association Executives (ASAE). Mr. Lebedev is also a member of the U.S. State Department’s Advisory Committee on International Economic Policy, and is a member of the advisory board of a litigation research and consulting firm.

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**Dr. Carol Henry, American Chemistry Council**

**Overview: Long-Range Research Initiative (LRI)**

Dr. Henry serves as Vice President for Science and Research at the American Chemistry Council (ACC). She directs and manages the ACC’s $25 million per year Long-Range Research Initiative that is designed to study the potential impacts of chemicals on health and the environment. She received her undergraduate degree in chemistry from the University of Minnesota and doctorate in microbiology from the University of Pittsburgh. In addition, Dr. Henry held postdoctoral fellowships in biochemistry at the Max Planck Institute in Germany, in biology at Princeton University, and biochemistry/cancer research at the Sloan Kettering Institute.

Prior to joining the American Chemistry Council in May 1999, Dr. Henry served as director of the Health and Environmental Sciences Department of the American Petroleum Institute (API) and as API’s chief scientist. Before joining API in 1997, Dr. Henry completed five years of public service, serving as associate deputy assistant secretary for Science and Risk Policy at the U.S. Department of Energy, and as director of the Office of Environmental Health Hazard Assessment at the California Environmental Protection Agency. Prior to that appointment, she was executive director of the International Life Sciences Institute’s Risk Science Institute.

A diplomate of the American Board of Toxicology, Dr. Henry is a member of the American College of Toxicology, of which she has been president, the Society of Toxicology, the American Association for Cancer Research, the American Association for the Advancement of Science, and the American Chemical Society. She served on the Board of Scientific Counselors of the National Toxicology Program and the EPA Clean Air Act Science Advisory Committee’s Blue Ribbon Panel on Oxygenates in Gasoline. She currently serves on the Board on Environmental Studies and Toxicology of the National Research Council, the Roundtable on Environmental Health Sciences, Research, and Medicine of the Institute of Medicine, the Chemical Sciences Roundtable of the National Research Council, the Strategic Environmental Research and Development Program’s Science Advisory Board, and as a Consultant to the EPA’s Science Advisory Board’s Executive Committee.
Dr. James Bus, The Dow Chemical Company

LRI Research Programs and Projects

Dr. Bus currently holds the position of Director of External Technology and serves as a member of the Leadership Team in the Toxicology and Environmental Research and Consulting group at the Dow Chemical Company in Midland, Michigan. Prior to joining Dow Chemical in 1989, he held positions of Associate Director of Toxicology and Director of Drug Metabolism at the Upjohn Company (1986-1989), Research Scientist at the Chemical Industry Institute of Toxicology (1977-1986), and Assistant Professor of Toxicology at the University of Cincinnati (1975-1977). Dr. Bus currently is Adjunct Professor of Pharmacology and Toxicology at Michigan State University and previously has held the position of Adjunct Associate Professor of Toxicology at the University of North Carolina.

In 1996-1997 Dr. Bus served as President of the Society of Toxicology, a 4000 member scientific society, and in 1986-1987 as President of the American Board of Toxicology, an organization which credentials practicing toxicologists. He is a current member of both the US Environmental Protection Agency Board of Scientific Counselors and the National Academy of Sciences Committee on Emerging Issues and Data on Environmental Contaminants. He also has served on the National Toxicology Program Board of Scientific Counselors, Bioassay Review Subcommittee (1996-2000), the ACGIH Chemical Substances TLV Committee (1993-2002), and as a Director of the International Union of Toxicology (1998-2001). Dr. Bus is the Co-Chair of the American Chemistry Council’s Long-Range Research Initiative, a $25 million per year industry-funded research program evaluating the potential health and environmental effects of industrial chemicals. In 2002, Dr. Bus was elected to the Board of Trustees of the International Life Sciences Institute (ILSI) Health and Environmental Sciences Institute, where he has Chaired the Emerging Issues Steering Committee. Since 1997, he has also been a member of the Board of Directors and Co-Chair of the Science Program Committee of the CIIT Centers for Health Research, a research institute founded by and primarily supported by the chemical industry.

Dr. Bus received his Ph.D. in Pharmacology from Michigan State University in 1975 and a B.S. degree in Medicinal Chemistry from the University of Michigan in 1971. His research interests have focused on mechanisms of chemical toxicity. In 1987 he was the recipient of the Society of Toxicology Achievement Award, granted for outstanding contributions to the science of toxicology by a young scientist. In 1999 he received the Robert A. Scala Award from the Environmental and Occupational Health Sciences Institute (Rutgers University) for outstanding contributions to toxicology by an industrial scientist, and in 2001 the Distinguished Alumnus Award from the Michigan State University Department of Pharmacology and Toxicology. He has authored or coauthored over 90 research papers, reviews, and books.
Dr. Melvin E. Andersen, CITT Centers for Health Research

Systems Biology and Dose-Response Assessment

Abstract

The emerging era in health effects research will witness full incorporation of systems biology as a guiding research paradigm. The hallmark of this paradigm is seamless integration of functional genomics, computational biology and bioinformatics to generate comprehensive biological hypotheses and provide integrative, quantitative tools for hypothesis testing and experimental design. In protecting public health an important systems biology-oriented research endeavor will be assessing the shape of dose-response curves at environmentally relevant exposure levels. Increasingly dose-response assessment for exogenous compounds will be based on more complete understanding of normal biological signaling pathways and of the magnitude of perturbations in these pathways caused by chemical exposures. Chemical exposures alter function of “molecular circuits” in cells by interfering with the normal function of biological components of these signaling pathways. For purposes of controlling complex biological systems, most molecular circuits have non-linear dose-response behaviors. These non-linear signaling behaviors eventually regulate large-scale cellular processes, e.g., commitment to cell division, cell differentiation, and phenotypic alterations, whose perturbations are more directly associated with pathology and disease. A systems biology approach focuses on the manner in which molecular level interactions of toxicants link to higher-level responses and eventually to health impairment. The CIIT Centers for Health Research have embraced this systems biology paradigm for our research program on health safety assessments for environmental chemicals, drugs and other stressors. This talk discusses opportunities and strategies for creating systems biology approaches for evaluating low dose risks of chemicals, especially of endocrine-active compounds (EACs) that target signal transduction pathways.

Biography

Dr. Mel Andersen is the Director, Division of Biomathematics and Physical Sciences, CITT Centers for Health Research, Research Triangle Park, NC. His responsibilities include imparting a systems biology emphasis to research on the health effects of environmental chemicals at the CIIT Centers for Health Research. He received his Bachelor of Science degree in Chemistry from Brown University and his Ph.D. in Biochemistry and Molecular Biology from Cornell University, Ithaca, NY. He is board certified in Industrial Hygiene and in Toxicology. From 1999-2002, Dr. Andersen was Professor of Environmental Health at Colorado State University, Ft. Collins, CO. From 1994-1998, he was Vice-President of the K.S. Crump Group of ICF Kaiser International Consulting and from 1971 to 1994 held positions in toxicology research and research management in the federal government (DoD and US EPA) and in private industry (including the Chemical Industry Institute of Toxicology). Dr. Andersen has developed computational models of the uptake, distribution, metabolism, and biological effects of drugs and toxic chemicals and applied these models in health safety assessments and quantitative health risk assessments. He is widely recognized for contributions in developing short-courses and computer demonstrations in pharmacokinetics and pharmacodynamic modeling over the past 15 years. His current research interests are in mathematical descriptions of control of genetic circuitry in the developing and adult organism and the dose response and risk assessment implications of these control processes.
Dr. Andersen is an author or co-author of over 230 papers and 30 book chapters. In June 2002, Dr. Andersen was recognized as a ‘highly cited’ scientist by the Institute for Scientific Information. He has received several awards for his professional contributions, including the Herbert Stokinger Award (American Conference of Industrial Hygienists, 1988), the George Scott Award (Toxicology Forum, 1993), the Kenneth Morgareidge Award (International Life Sciences Institute, 1989), and both the Frank R. Blood (1982) and Achievement Awards (1984) from the Society of Toxicology.
Dr. Rory B. Conolly, CITT Centers for Health Research

Formaldehyde and Chloroform: Rodents Cancers, Human Risks?

Abstract
Toxicology is both blessed and cursed by the fact that it is easier to demonstrate adverse effects in laboratory animals than know what the animal effects mean for people. Historically, laboratory animals have been the main option for characterizing chemical hazards and dose-response behaviors. Animal experiments usually can't, however, be directly confirmed in people, and accurate extrapolation of animal results to people presents technical challenges that are only now being seriously addressed. Twenty-first century toxicology has inherited a legacy of human health risk assessments, based on animal data, which are arguably protective of the public health and, at the same time, probably wildly inaccurate. Inaccurate regulations burden society with unnecessary economic costs and lost access to useful products. We are now developing a toolbox to address these concerns while maintaining and even improving confidence that the public's health is protected. The toolbox contains a rat, some human cells, a test tube, and a computer. The rat, human cells and test tube represent research on mechanisms of toxic action that tell us what the chemical does to the organism and, just as importantly, how the organism responds to the chemical. In fact, at low, environmentally-relevant levels of exposure, the ability of the organism to generate an adaptive response may be the primary determinant of the shape of the dose-response curve. The computer represents our ability to systematically organize large amounts of data, develop quantitative descriptions of mechanisms of toxic action, and use simulation to predict dose-response behaviors. The power of the computer lies in its ability to integrate all of the relevant mechanistic data in generating these predictions. In this regard computers are superior to human intuition. In this presentation the use of mechanistic research and computer modeling to estimate human cancer risks for formaldehyde and chloroform are described. The results of assessments obtained with the new toolbox are contrasted with earlier assessments. Additional refinements possible from the study of mechanisms at the molecular level using the new high throughput technologies are briefly considered.

Biography
Rory Conolly is a Senior Scientist and Director of the Center for Computational Biology & Extrapolation Modeling at the CIIT Centers for Health Research. His main research interest is human health risk assessment, with an emphasis on reducing uncertainty in risk assessment through development of quantitative, mechanism-based exposure-response models.

Dr. Conolly received formal training in biology and biochemical toxicology and became interested in physiologically based pharmacokinetic models in the early 1980's. He worked initially on the biochemical mechanism of hepatic DNA damage by 1,2-dichloroethane and on the ototoxicity of toluene. He has developed simulation models and directed laboratory studies for a variety of chemicals, including organophosphates and halogenated hydrocarbons, worked on stochastic simulation models to examine the roles of cellular division and apoptosis in chemical carcinogenesis, and on several physiologically based pharmacokinetic models, including models describing pregnancy and lactation. More recently, he has played a central role in the development of a new mechanism-based cancer risk assessment for formaldehyde that uses advanced dosimetry and tissue response modeling.

Dr. Conolly was President of the Society of Toxicology (SOT) Biological Modeling Specialty Section (2000-2001) and of the SOT Risk Assessment Specialty Section (1997-1998) and...
was a member of the SOT Risk Assessment Task Force (1998 - 2000). He is an Adjunct Professor of Biomathematics at North Carolina State University, a Faculty Affiliate, Department of Environmental and Radiological Health Sciences, Colorado State University and has three times received awards from the Risk Assessment Specialty Section (1991, 1999, 2003) for the best presentation in risk assessment at the SOT Annual Meeting. Dr. Conolly maintains an active interest in teaching, having most recently (February 2003) given a 3-day course on simulation modeling and risk assessment in Germany and lectures on risk assessment at North Carolina State University. In addition to the SOT, he is a member of the Society for Risk Analysis and has been a diplomate of the American Board of Toxicology since 1980.

Dr. Conolly was born in London, England and raised in Canada and the United States. He received a bachelor's degree in biology from Harvard College in 1972, a doctorate in physiology/toxicology from the Harvard School of Public Health in 1978, and spent a post-doctoral year at the Central Toxicology Laboratory of Imperial Chemical Industries, PLC, Cheshire, England. He was a member of the Toxicology Faculty at The University of Michigan School of Public Health from 1979 through 1986, and worked with the U.S. Air Force Toxic Hazards Research Division, Wright-Patterson Air Force Base, Ohio from 1986 until 1989, when he joined CIIT.
Dr. James Shine, Harvard School of Public Health

**Improving Risk Assessment of Contaminated Sediments: Accounting for Speciation, Multiple Routes of Exposure, and Complex Mixtures**

**Abstract**

Humans rely on water for many reasons: as a source of drinking water, a source of food, for commerce, recreation, and as a receptacle of human, industrial, and agricultural wastes. Our ability to best manage these competing needs relies on a sound understanding of how basic ecological processes affect the transport, fate, and effects of anthropogenic stressors released to the environment. Many contaminants released to aquatic ecosystems, including heavy metals, are particle reactive and accumulate in sediments. The aim of this project is to better characterize the geochemical cycling of metals in sediments with respect to their bioavailability and subsequent effects on human and ecological health. A complicating factor is that contaminants such as heavy metals are often released to the environment as complex mixtures. Competitive geochemical interactions amongst metals can both enhance or suppress the effects of an individual metal depending on the nature of the overall metal mixture. Through a combination of basic laboratory experiments on metal geochemistry and multivariate statistical modeling of sediment toxicity data, this project is improving our ability to understand these competitive interactions. Determining risks associated with contaminated sediments has become an important issue for environmental decision makers. The goals of this project are to develop tools that allow informed decisions to be made concerning the release of contaminants into aquatic ecosystems, the ability to determine the presence of adverse effects, and to determine clean-up levels (if necessary) protective of human and ecological health.

**Biography**

Dr. Shine is currently the Winkler Assistant Professor of Aquatic Chemistry in the Department of Environmental Health at the Harvard School of Public Health. He has a B.S. in Biology from St. Lawrence University, and a Ph.D. in Environmental and Coastal Ocean Sciences from the University of Massachusetts. His research interests include studies of the biogeochemical factors affecting the transport, distribution, fate, and effects of contaminants released into aquatic ecosystems. In addition to studying water and health related issues in places such as Boston Harbor and New Bedford Harbor, Dr. Shine is part of a team of scientists who have been charged by the Intergovernmental Oceanographic Commission (part of UNESCO) to develop and disseminate tools that can used in developing nations to assess aquatic ecosystem health. Dr. Shine is also the director of Harvard's Program in Water and Health, a student-centered program designed to foster interdisciplinary basic and applied research in water and health.
Day I Presentations:
Keynote Speaker

Dr. Samuel H. Wilson, National Institute of Environmental Health Sciences

Exposure Analysis: An Integral Part of Disease Prevention

Biography  Samuel H. Wilson is Deputy Director of the National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), and of the National Toxicology Program. Dr. Wilson came to NIEHS in this capacity in 1996, where he has been instrumental in new NIEHS programs in genomics, toxicogenomics, children's health, and minority institutions' research. Dr. Wilson has strengthened partnerships between NIEHS and other federal agencies concerned with environmental health, including the Centers for Disease Control and Prevention and the Environmental Protection Agency. He has worked with the Institute of Medicine to develop a Roundtable promoting broad-based discussions and long-term strategic planning on issues relevant to environmental health, research, and medicine and with the National Research Council on issues relevant to toxicogenomics.

Dr. Wilson received his graduate and postdoctoral training in medicine and biochemistry at Harvard University (M.D., 1968) and the NIH. He began his career as a Principal Investigator in 1970 at the NIH in the National Cancer Institute's Laboratory of Biochemistry. In 1991, Dr. Wilson moved to The University of Texas to establish the Sealy Center for Molecular Science.

Dr. Wilson's recent activities include membership on the Biochemistry Study Section at the NIH and numerous other federal agency advisory teams. He has served as a scientific advisor to several private foundations and other groups involved in supporting biomedical research. He is Associate Editor of DNA Repair and a member of the editorial boards of the Journal of Biological Chemistry and Annual Review of Medicine. Dr. Wilson is currently a Principal Investigator in the Laboratory of Structural Biology at NIEHS. He has authored and co-authored over 260 scientific publications and has been editor of four reference volumes.
Day I Presentations:
Poster Session Organization

Ms. Cheryl Morton, American Chemistry Council

Meeting Organizer

Ms. Morton serves as Managing Director of the LRI. Prior to joining the Council, Ms. Morton was the Director of Regulatory and Technical Affairs at the Synthetic Organic Chemical Manufacturers Association (SOCMA). At SOCMA, she managed the government relations’ staff and served as SOCMA’s expert on compliance assistance and regulatory advocacy related to the Toxic Substances Control Act (TSCA). Earlier in her career, she was Director of Environmental Affairs at a public relations firm in Washington, D.C., where she managed three associations focusing on air, water, and hazardous waste. Also, she worked on U.S. Environmental Protection Agency contract projects at ENVIRON and Booz, Allen and Hamilton. Ms. Morton received a B.S., Environmental Science and B.S., Chemistry, George Washington University, where she has taken selected graduate courses in the Regulatory Affairs Program.
Day I Plenary Session:
Current National Exposure Research Activities

Dr. Tina Bahadori, American Chemistry Council

Exposure Research: The LRI Perspective

Abstract
The ultimate goal of the LRI is to increase knowledge of the potential impacts that chemicals may have on the health of human and wildlife populations and the environment. Achieving this goal requires that the LRI provide a sound scientific foundation for input into the risk equation and in particular information about the lesser-known exposure component. Exposure assessment requires the integration of methods, measurements, and modeling. Although all three areas need research, the LRI has chosen to focus on development and interpretation of methods, which will enable the program to have a larger impact, given the scope of other organizations’ exposure programs. LRI research has the potential to advance exposure research through (1) improved methods focus area as more cost-effective methods to measure exposure are developed, (2) susceptibility factors focus area as factors leading to higher-than-usual exposures (and hence risk) are identified, and (3) chemicals in the environment focus area as exposure measurements are incorporated into the exposure and verification of model development. This presentation will provide an overview of LRI’s exposure research program as a theme cutting across all three Focus Areas.

Biography
Dr. Bahadori is a Senior Scientist and serves as a Senior Director for the LRI, with specific responsibilities in the areas of Exposure and Risk Assessment. Prior to joining the Council, she was the Manager, Air Quality Health Integrated Programs, at the Electric Power Research Institute (EPRI). In addition to managing specific projects, she was responsible for the design, implementation, and promotion of collaborative research, with particular emphasis on policy and regulatory decision-making. At Arthur D. Little, Inc., where she was a Consultant in the Environmental Risk Management Unit, she assisted clients with technical and management problems related to environment, health, and safety matters. She holds a doctorate in Environmental Science and Engineering from the Harvard School of Public Health. From MIT, she was awarded a M.S., Chemical Engineering and Technology and Policy and B.S., Chemical Engineering, and B.S., French Literature.
Dr. Debbie Bennett, Harvard University

Rapateur

Dr. Bennett is an assistant Professor of Environmental Health and Risk Assessment in the Departments of Environmental Health and Health Policy and Management. Dr. Bennett's research focuses on the fate and transport of chemicals in a multimedia environment within the context of environmental risk assessment.

Her current research interests include exposure to pesticides, both from indoor and agricultural uses, and the use of multimedia models for Life Cycle Impact Assessments. She has developed methods for quantifying the spatial range, temporal persistence and population based dose of organic pollutants in a multimedia environment. Additionally, she has developed a classification system for persistent pollutants and examined the use of long range transport models in the context of regulatory decisions through a model comparison.

Dr. Bennett is also the first recipient of the International Society of Exposure Analysis (ISEA) Early Career Award sponsored by the American Chemistry Council. Her research related to this award will focus on “Assessing Human Exposure to Hazardous Air Pollutants (HAPs).” An outcome of the research will be the development of a model to help provide insight on which sources and locations lead to higher levels of exposure for each HAP studied. This information will enable better decisions when developing risk management strategies as well as identifying data gaps that should be filled to improve our estimates of population exposure.

Dr. Bennett received her M.S. and Ph.D., in Engineering-Mechanical Engineering at the University of California at Berkeley and a B.S., in Mechanical Engineering, magna cum laude, from the University of California, Los Angeles.
Day I Plenary Session:
Current National Exposure Research Activities

Dr. Petros Koutrakis, Harvard School of Public Health

Assessing Human Exposure

Abstract
Exposure is a critical step in our efforts to link human health effects to pollution sources. Often cohort and ecological epidemiological studies suffer from lack of accurate exposure data. Use of untested exposure factors of models may hinder our ability to interpret subtle, but very important health outcomes. Similarly, mechanistic studies will benefit from comprehensive assessments, which will make it possible to use realistic exposure metrics in laboratory-controlled experiments.

In my presentation, I will focus on the importance of exposure assessment to enhance our understanding about particle health effects. My presentation will focus on criteria pollutant exposures because of my familiarity with this topic, and because particle exposures have been investigated more than other pollutants. However, my observations and conclusions can be easily extrapolated to other pollutants.

The Donora, PA and London air pollution episodes provided us with solid evidence for the mortality and morbidity effects associated with the inhalation of air pollutants. In spite of the substantial improvements of air quality that have taken place over the last forty years, there is still evidence suggesting health effects occurring at very low particulate and gaseous pollutant levels. Over this half-century span the exposure assessment has become a critical component of epidemiological studies. A mere observation of the atmosphere in London would be sufficient to establish the association between excess mortality and coal combustion in Donora. Today in spite of the use of personal monitors, comprehensive time activity diaries, and specific analytical methods, establishing this causal association between health outcome and source type remains a challenging task.

Visual observations and personal monitoring may represent the archaic and the modern extremes of the exposure assessment spectrum. A plethora of widely used approaches have been employed including: Central Site Monitoring that is assumed to represent a city-wide population exposure; Multiple Site Monitoring within a city; Source Receptor Air Quality Models that expand from local to regional scales; Satellite Data; and Geographical Information Systems.

Both the increasing wealth and improving quality of data have resulted in the proliferation of air pollution health effect studies as reflected in two recent PM NAAQS reviews in 1997 and 2002. As a result of the 1997 PM NAAQS review, a number of scientific questions on exposure assessment arose such as: What is the relationship between human exposures and outdoor concentrations? To what extent can single outdoor monitoring represent population exposure? What is the impact of outdoor environment exposure? Exposure assessment studies have addressed these issues and have provided support to time-series epidemiological studies. However, substantial intra- and inter-personal variability in exposures were observed. This explained the variability of the impact of outdoor and indoor sources.

The varying impact of outdoor pollutions to different individuals and, therefore, populations is of paramount importance. This implies that for the same outdoor pollution levels, personal exposure to outdoor particles may differ by individual (e.g., the fraction of outdoor particles to which individuals are exposed to varies between approximately 0.2 to 0.9). A large fraction of this variability was explained by home ventilation (air exchange...
rate). Since home ventilation is a function of climatic conditions and housing characteristics, one would expect that population exposure will vary by geographical location and season.

These findings have been critical in our effort to explain variability of risk factors reported by epidemiological investigations. Furthermore, exposure studies have addressed the role of gaseous co-pollutant exposures and have examined whether criteria gases are co-founders or surrogates of particle exposure. Finally, the implications of the recent exposure assessment findings are very important for the design of future populations and cohort chronic health effect studies. Preliminary data suggest that ranking populations or cohort chronic exposures by outdoor concentrations may not be accurate and that additional exposure factors should be used to provide accurate populations or cohort exposures.

In conclusion, exposure assessment does not only provide values on exposures but also helps to interpret health studies and to design new hypothesis for new ones.

Biography  Petros Koutrakis is Professor of Environmental Sciences, Director of the Environmental Science and Engineering Program, and the Director of the Environmental Chemistry Laboratory at the Harvard School of Public Health. He received his Ph.D. in environmental chemistry from the University of Paris. His research interests include human exposure assessment, ambient and indoor air pollution, environmental analytical chemistry, and environmental management. He is Technical Editor-In-Chief of the Journal of the Air and Waste Management Association, consultant to the EPA Science Advisory Board, and an advisor to the International Monitoring of Protected Visual Environments (IMPROVE), Pan American Health Organization (PAHO), World Health Organization (WHO), and the United Nations Environment Program (UNEP). He has served on several EPA review panels and chaired the EPA Review Panel for Research Proposals on Ambient Particle Modeling.
Day I Plenary Session:
Current National Exposure Research Activities

Dr. Thomas E. McKone, Univ. of California, Berkeley/Lawrence Berkeley National Lab.

Persistence, Proximity, and Mobility: Tracking Human Exposure to Multimedia Pollutants

Abstract
Widespread observations of organic pollutant compounds in the environmental and in human tissue have motivated research on more accurate characterizations of chemical transport over indoor, local, regional, continental, and even global scales. In this talk, I will provide an overview of the multimedia mass-balance approach to pollutant fate and exposure evaluation and illustrate how this approach relates to environmental health research. Because of the growing size and complexity of multimedia exposure models and datasets, there is a need for simple but informative exposure metrics. An example is intake fraction (iF)—the ratio of human intake to emissions—an extensive metric that is a function of persistence, proximity, and mobility. The overall persistence (Pov) is the residence time of a contaminant in a defined environment, such as indoor air, an urban air shed, a watershed, etc. Because of international efforts to regulate persistent organic pollutants (POPs), assessment of Pov has been an area of active research. Proximity defines the spatial relationship between a chemical release and an exposure medium. For the inhalation pathway proximity is determined by the exposed individual’s location relative to sources. But for dermal contact and specifically for ingestion, proximity becomes more problematic but still tractable. Mobility has been defined as the expected speed of the pollutant as it moves from source to receptor. For pollutants that are “sticky” (tending to partition to and from other media) mobility depends on complex mass exchange. We will consider how common parameters such as persistence, proximity, and mobility can be used as tools to classify pollutants and evaluate model performance.

Biography
Thomas E. McKone is a Senior Staff Scientist and Group Leader for Exposure and Risk Analysis at the Lawrence Berkeley National Laboratory and an Adjunct Professor and researcher with the School of Public Health at the University of California, Berkeley. His research interests include the development and use of multimedia exposure models in health-risk assessments, chemical transport and transformation in the environment, and the health and environmental impacts of energy, industrial, and agricultural systems. In addition to his research and teaching activities with the University of California, Dr. McKone is active in other research, regulatory, and professional organizations. He has served on several committees of the National Academy of Sciences and served six years as a member of the EPA Science Advisory Board. He is past-president of the International Society of Exposure Analysis (ISEA) and has been on consultant committees for the International Atomic Energy Agency, the World Health Organization, and the Food and Agriculture Organization. Dr. McKone received his M.S. and Ph.D. in engineering from the University of California at Los Angeles.
Abstract  

The goal of NERL’s Exposure Research Program is to improve the scientific basis for conducting human exposure assessments that are part of the EPA’s risk assessment, risk management and compliance process. Overall, we aim to address aggregate and cumulative exposures that pose the greatest risks to the American public. The program addresses exposures for the general population and susceptible subpopulations including children, asthmatics, and the elderly. A systematic approach is taken to planning and implementing our research. First, the highest priority regulatory needs for exposure data are identified. An iterative process between method development, measurements, and modeling is then used to develop and conduct the research. Preliminary models are developed to identify key data gaps and uncertainties. Specific laboratory or field measurement studies are designed to:

1. Identify those chemicals, pathways, and activities that represent the highest potential exposures;  
2. Systematically identify the data (exposure factors) required to estimate exposure by each route;  
3. Develop approaches for generating the required data; and  
4. Apply these approaches in field studies to develop data on exposures and the relevant exposure factors.

Currently, exposure measurement studies are addressing two critical areas: children’s aggregate exposures to pesticides and inhalation exposure to PM, PM constituents, and air toxics. Outputs of current studies will be described. Details of new studies in both areas will also be provided.

Disclaimer  

This is an abstract of a proposed presentation and does not necessarily reflect US EPA policy. The actual presentation has not been peer reviewed by EPA. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Biography  

Dr. Sheldon is Associate Division Director for the Human Exposure Program within EPA’s National Exposure Research Laboratory. She is responsible for strategic planning and implementation of research to evaluate and quantify human exposures to chemicals from all routes and pathways. While at EPA, Dr. Sheldon has developed comprehensive research programs to evaluate exposure to particulate matter and air toxics. She has also been responsible for developing a research program that addresses the major uncertainties associated with children’s exposure to pesticides and other chemical contaminants. Prior to joining EPA, Dr. Sheldon was a Senior Manager and research scientist at Research Triangle Institute. Dr. Sheldon’s research at RTI focused on the developing methods for the analysis of trace levels of organic pollutants and applying these methods to exposure assessments. Dr. Sheldon has conducted several large probability-based exposure monitoring programs for VOCs, PAHs, phthalates, particles, and gases directed toward evaluating personal exposures or indoor exposures in homes and schools. She has conducted additional studies to evaluate infants’ and children’s exposure to pesticides and lead, commuters’ exposure to VOCs, particles, PAHs, and gases, farm workers’ exposures...
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to pesticides, and exposures to pollutants through the dietary route. She has also provided support for several epidemiology studies supported by National Environmental Institute and Environmental Health Sciences and National Cancer Institute to evaluate the relationship between health outcomes and exposures to pesticides, PCBs, and PAHs. Dr. Sheldon holds degrees in chemistry and environmental chemistry from Cornell University and the University of Michigan. She was a Post Doctoral Fellow at the Massachusetts Institute of Technology.
Abstract

Estimation of exposures of children and adults to air toxics or multimedia pollutants require careful consideration of sources and concentrations of pollutants that may be present in different media, as well as various routes and pathways of exposures associated with age-specific activities of individuals. In recent years, a number of probabilistic inhalation or aggregate exposure models have been developed by various researchers for estimating exposures to selected chemicals from different routes and pathways. Cumulative exposure models, dealing with aggregate exposures from more than one chemical are, however, still mostly in developmental stage. The EPA's Office of Research and Development (ORD), National Exposure Research Laboratory (NERL) has developed a probabilistic model (Stochastic Human Exposure and Dose Simulation Model, or SHEDS) that predicts the variability in the distribution of personal exposures and doses within a population cohort, as well as the uncertainty in the model estimates. The SHEDS model framework has initially been developed to study general population exposures to fine Particulate Matter (PM2.5) and children's exposure to pesticides. At the present, the SHEDS-Pesticides models include the inhalation and dietary ingestion routes in addition to dermal contact and non-dietary ingestion. SHEDS-PM (i.e., particulate matter and its associated constituents) and SHEDS-ATOX (i.e., air toxics) models, which are currently either being refined or developed, use the same modeling approach as the SHEDS-Pesticides model, however the primary focus is on inhalation exposure and dose. A user-friendly interface has been developed for the aggregate SHEDS-Pesticides and SHEDS-PM model with both exposure researchers and regulators in mind as potential users. SHEDS and other aggregate or cumulative pesticide exposure models still need rigorous evaluation and independent verification against carefully designed field studies. All of the exposure models suffer from limitations of available input information on critical exposure factors, especially for children. In general, models need to identify which inputs or parameters are of special concern for future model refinements or further sensitivity analysis. This information will in turn assist the design of future field exposure and biomonitoring studies that will be used in refining or evaluating the current exposure models. In order to develop more robust models with more complete input data, repeated or longitudinal concentration or residue measurements, time-activity data, and frequency of chemical-specific product use information in homes, day care centers/schools, commuting and other important microenvironments are also needed. Finally, the form of model outputs that are most useful to regulatory and scientific agencies and to the public also needs to be identified.

Disclaimer: This work has been wholly funded by the United States Environmental Protection Agency. It has been subjected to Agency review and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Biography

Dr. Halûk Özkaynak is the Senior Science Advisor at the U.S. Environmental Protection Agency's (EPA) National Exposure Research Laboratory (NERL), Human Exposure and Atmospheric Sciences Division in the Office of Research and Development (ORD). The principal responsibilities of his position include, providing leadership in developing, communicating, and implementing EPA/ORD’s research plans in the area of Human Exposure Source-to-Dose modeling. Current programs in this area at ORD/NERL include, measurement and modeling research on assessing population exposures to particulate...
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matter, air toxics and multimedia multipathway pollutants, such as pesticides. Dr. Özkaynak is presently the Co-Chair of the Chemical Exposure Workgroup of an interagency study in the US for the planned National Children’s Study (NCS). He is also the Co-Chair of EPA’s Assessment Factors Workgroup under the Information Guidelines Committee. Prior to joining EPA in 1998, Dr. Özkaynak was a Lecturer at the Department of Environmental Health of the Harvard School of Public Health in Boston. His recent research at Harvard included directing a multi-year environmental epidemiology study in Russia and participating in various exposure assessment and community studies, including the National Human Exposure Assessment Survey (NHEXAS) sponsored by the U.S EPA. Dr. Özkaynak is the Past President of the International Society of Exposure Analysis (ISEA).
Dr. Larry L. Needham, Centers for Disease Control and Prevention

Role of Biomonitoring in Human Exposure Assessment

Abstract

There are various means for assessing either an individual’s or a population’s exposure to environmental toxicants. One such method epidemiologists sometimes use is based on questionnaire information on one’s residential proximity to the source (e.g., a lead smelter) and how much time one comes in contact with that environment (based on lifestyle/activity pattern). Other times they combine this information with environmental levels in the matrix of interest (air, food, water, or soil). Although these approaches are useful, they do not provide quantitative information as to how much of the toxicant actually is absorbed into the body. Our preferred approach is to measure the internal dose—that is, the level of the toxicant, its primary metabolite(s), or reaction product (an adduct) in a biological tissue—and then combine this internal dose level with the questionnaire data. This approach assesses the exposure by all routes and pathways, which is needed for quantitative epidemiologic and risk assessment studies.

We have used this approach for assessing human exposure to a variety of environmental toxicants, including pesticides (both persistent and nonpersistent), volatile organic compounds, industrial chemicals and by-products (PCBs, dioxins, and furans), metals, and constituents in personal care products. In addition to assessing human exposure and relating that data to potential adverse health effects, we have used these measurements to assess trends in human exposure, to determine populations at risk, to judge the effect of legislation and public health statements, and to determine “background” levels of persistent (either because of long half life or continuous emission) environmental toxicants in the general population.

The data in our Second National Report will be discussed along with its applications in epidemiological studies. Our experiences in assessing human exposure via biomonitoring and our plans for the future will be described in greater detail.

Biography

Larry L. Needham, Ph.D., is Chief of the Organic Analytical Toxicology Branch of the National Center for Environmental Health, Centers for Disease Control and Prevention (CDC). He has served at CDC for over 26 years in the area of assessing human exposure to environmental chemicals through biological monitoring. Dr. Needham has authored or coauthored about 250 publications in this area, with special emphasis on polychlorinated dibenzo-p-dioxins, furans and biphenyl; pesticides; phthalates; phytoestrogens; and inorganic elements. Dr. Needham was the recipient of this year’s CDC award for outstanding scientific leadership. Dr. Needham serves on the Advisory Board for many scientific organizations and studies. In addition, he is President-elect of the International Society of Exposure Analysis.
Abstract
On a macroscopic scale, the respiratory tract can be divided into three regions: extrathoracic (nares through the larynx), tracheobronchial (trachea to terminal bronchioles), and alveolar. Removal of inhaled material in the extrathoracic region serves to lessen the insult to the sensitive tissues of the lower respiratory tract. The combination of complex geometry of the passages and patterns of airflow to various locations within the nose result in different removal efficiencies for various sizes of particles and for various types of gases. The tracheobronchial airways in the human lung are dichotomous in nature. Heterogeneity of branching patterns leads to variability in particle deposition in individual tracheobronchial paths as well as in acini. This variation in path length, coupled with variability in the volume of the acini attached to terminal bronchioles, also has implications for the extent to which exposure to low concentrations of gaseous pollutants can result in patchy lesion distributions in the alveolar region. Scientists at the CIIT Centers for Health Research are developing dosimetry models that incorporate (1) anatomy and physiology, (2) the physics of gas and particle transport, and (3) mechanisms for removal and transport within respiratory tissue that aid inter- and intra-species dosimetric comparisons and enable exposure-dose-response relationships to be established in risk assessments of inhaled material. This presentation will (1) provide information on various dose metrics related to the deposition and clearance of particles and (2) highlight the features of a user-friendly software program for particulate dosimetry that can assist researchers in linking human exposures to respiratory tract responses.

Biography
Fred J. Miller, Ph.D. is currently Vice President for Research at the CIIT Centers for Health Research (CIIT). He has been at CIIT since February, 1991. Dr. Miller received a B.A. and M.S. in Statistics from the University of Wyoming. In 1968, he began a career as a commissioned officer in the U.S. Public Health Service (PHS). He received a Ph.D. in Statistics from North Carolina State University in 1977; his doctoral research was on the transport and removal of ozone in the lungs of animals and humans. During his career with the U.S. Environmental Protection Agency, Dr. Miller served as Director of the Health Effects Research Laboratory's Inhalation Toxicology and Environmental Toxicology Divisions. Upon retirement from the PHS in 1989, Dr. Miller joined the faculty of Duke University Medical Center, continuing his long-standing interest in extrapolation modeling through his capacity as an Associate Director of the Duke Center for Extrapolation Modeling.

Dr. Miller's primary research interests include pulmonary toxicology, respiratory tract dosimetry of gases and particles, lung physiology and anatomy, extrapolation modeling, and risk assessment. He is internationally recognized for his research on the dosimetry of reactive gases. Dr. Miller is active in professional societies and consulting on environmental health issues. The author or co-author of more than 150 publications, Dr. Miller received a number of Scientific and Technical Achievement awards from EPA and is the recipient of the PHS' Outstanding Service Medal. He currently serves on EPA's Clean Air Scientific Advisory Committee. He has also been an advisor to various other public organizations and currently chairs the Science Advisory Committee for the National Jewish Medical and Research Center's (Denver, Colorado) Environmental Lung Center.
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Day II Presentations

Dr. Zachary Wong, ChevronTexaco Energy Research and Technology Company

Chair

Zachary Wong is Manager of Toxicology and Health Risk Assessment at ChevronTexaco Energy Research and Technology Company. Dr. Wong has held a variety of leadership positions within the ChevronTexaco group of companies since 1978, gaining over 25 years of expertise in human and environmental toxicology, health and safety management, health risk assessments, toxicology research and testing, economic analyses, strategic planning and regulatory toxicology. For the past ten years Dr. Wong has been an instructor at the University of California, Berkeley Extension, teaching Toxicology and Project Management. He was honored as an instructor of the year in 2002. Since 1999 he has been a member of the Strategic Science Team of the American Chemistry Council. Dr. Wong gained a B.S. in Zoology from the University of California at Davis, and a Ph.D. in Environmental Toxicology and Pharmacology from the University of California, Davis. He is also a Diplomate, American Board of Toxicology (DABT).

Keynote Speaker

Dr. Paul Gilman, U.S. Environmental Protection Agency

EPA’s Programs on Use and Application of Exposure in Risk Assessment/Management

Biography

In April 2002, Dr. Gilman was sworn-in to serve as the Assistant Administrator for the Office of Research and Development, which is the scientific and technological arm of the Environmental Protection Agency. In May 2002, he was appointed the Agency Science Advisor. In this capacity, he is responsible for working across the Agency to ensure that the highest quality science is better integrated into the Agency’s programs, policies and decisions.

Before his confirmation, he was Director, Policy Planning for Celera Genomics in Rockville, Maryland. Celera Genomics, a bioinformation and ORD Calendar drug discovery company, is known for having decoded the human genome. In his position Dr. Gilman was responsible for strategic planning for corporate development and communications.

Prior to joining Celera, Dr. Gilman was the Executive Director of the life sciences and agriculture divisions of the National Research Council of the National Academies of Sciences and Engineering. The National Research Council is the operating arm of the National Academies which were chartered to provide independent advice to the government in matters of science and engineering. Dr. Gilman's divisions focused on risks to health and the environment, protection and management of biotic resources, and practical applications of biology, including biotechnology and agriculture.

Before joining the National Research Council, Gilman was the Associate Director of the Office of Management and Budget (OMB) for Natural Resources, Energy, and Science. There he coordinated budget formulation, regulatory, and legislative activities between agencies such as the Environmental Protection Agency, National Science Foundation, Agriculture, and Energy with the Executive Office of the President.
Day II Presentations:
Keynote Speaker

Dr. Gilman served as Executive Assistant to the Secretary of Energy for technical matters before joining the OMB. His responsibilities included participating in policy deliberations and tracking implementation of a variety of programs, including the Department's environmental remediation and basic science research.

Gilman has 13 years of experience working on the staff of the United States Senate. He began that time as a Congressional Science Fellow sponsored by the American Association for the Advancement of Science in the office of Senator Pete V. Domenici. Later, as the Staff Director of the Subcommittee on Energy Research and Development, he was involved in the passage of the Nuclear Waste Policy Act of 1982 and oversight of energy technology and environmental research. Later he served as the chief-of-staff for Senator Domenici.

Dr. Gilman matriculated at Kenyon College in Ohio and received his A.B., M. A., and Ph.D. degrees in ecology and evolutionary biology from Johns Hopkins University, Baltimore, Maryland.
Dr. Julie Kimbell, CITT Centers for Health Research

Effects of Interindividual Differences in Human Nasal Anatomy on Upper Respiratory Tract Airflow and Inhaled Gas Uptake

Abstract

Differences in nasal anatomy and respiratory airflow patterns among different human individuals may cause significant differences in the regional dose of inhaled gases within the nasal passages and subsequently the lung. Information on the effects that anatomical variations have on nasal uptake and identification of sensitive subpopulations is needed to decrease uncertainty in risk assessments. Computational fluid dynamics (CFD) can quantify the effects of anatomical variation on nasal uptake and help reduce the reliance on default uncertainty values. Efforts in this project focus on estimating the variability of nasal uptake through simulation of a number of individuals. The generation of computational grids from MRI scan data was semi-automated and three new CFD models were constructed, including an adult female. The construction of a nasal CFD model from CT scans of a 4-year-old boy is currently in progress. Simulations in adults indicated that there are interindividual differences in bulk airflow patterns in the nose. Overall uptake was not highly sensitive to the ratio of total nasal surface area to volume, with results suggesting that uptake comparisons should be made regionally within the nose. Correlation of uptake with anatomical features will be used to identify potential determinants of sensitivity and will aid in the identification of at-risk subpopulations. Together with an understanding of regional tissue susceptibility, this opportunity to quantitatively evaluate the effects of interindividual differences in nasal anatomy on airflow and uptake helps provide a sound scientific basis for reduction of the need for a 10-fold sensitive human subpopulation uncertainty factor.

Biography

Julie Kimbell received her B.A. in mathematics with a minor in music from Middlebury College in 1982. She attended graduate school at Duke University, receiving an M.A. in mathematics in 1984 and a Ph.D. in differential geometry in 1988. In 1989 she became a Postdoctoral Fellow at the Chemical Industry Institute of Toxicology (now CIIT Centers for Health Research), working with Drs. Tom Starr, Mel Andersen, Kevin Morgan, and Fred Miller on regional dosimetry of inhaled formaldehyde in the nasal passages of laboratory animals and humans. In 1992 she became a staff scientist at CIIT, and since 1993 has been a project leader on studies that use three-dimensional, computer reconstructions of the nasal passages to understand the effects of nasal anatomy and physiology on respiratory airflow, inhaled gas uptake, and particle deposition.
Abstract

The objective of our research is to improve statistical and experimental methods for assessing interactions within mixtures of endocrine-active compounds using in vitro "reporter" assays and the in vivo immature rodent uterotrophic model. In initial in vitro studies, large experimental designs (64 treatment groups) were used to evaluate ternary mixtures, and responses compared to those predicted from additivity models. These studies established our ability to detect both additive and non-additive interactions. In addition, we found that interactions differ dramatically at high vs. low doses. Our current research is focused at characterizing the significance of exposure to low doses of synthetic estrogen (SE) when it occurs in the presence of relatively high doses of dietary phytoestrogens (PE). This research will help address the adequacy of uncertainty factor approaches in risk assessment. Rigorous statistical models are being employed to determine if low levels of the SE can (a) alter the response threshold for the PE (both in vitro and in vivo) and/or (b) result in a non-additive interaction (i.e., antagonistic or synergistic). An examination of changes at the molecular level (e.g., gene expression) will also provide mechanistic data that could be correlated to observed responses. Interim results suggest that additivity of SE and PE come into play only when the individual chemicals are present at doses very close to or above their individual NOELs. Supported by the American Chemistry Council and The Dow Chemical Company.

Biography

Dr. Grantley Charles currently holds the position of Research Specialist in the Molecular and Cellular Biochemical Toxicology group within the Dow Chemical Company. His research is currently focused in the area of molecular toxicology screening methodologies, primarily in an in vitro context. More specifically, his current work (funded in part by a grant from the American Chemistry Council), involves the investigation of the interactions of the components of endocrine-active mixtures in both in vitro and in vivo model systems. He earned his B.Sc in Chemistry/Biochemistry at the University of West Indies and a Ph.D. in Pharmacology/Toxicology at the University of Florida under Dr. Kathleen Shiverick. He conducted postdoctoral research in the Developmental and Reproductive Toxicology group at Dow Chemical under Dr. Edward Carney, and later transferred to his current full time position. He is currently a member of the Society of Toxicology, a Diplomate of the American Board of Toxicology, and recently served on the recently concluded ICCVAM-NTP Expert Panel for the Evaluation of in vitro Endocrine Disruptor Test methods.
Mr. Larry Brewer, Springborn Smithers Laboratories

Development and Verification of Field-Deployable Methods for Evaluating Exposure and Effects of Endocrine-Active Substances in Wild Bird Populations

Abstract

There is a general concern that low amounts of pervasive chemicals in the environment may be affecting songbirds through estrogenic effects, thus changing their mating behaviors and reproductive output. However, methods for monitoring and/or detecting such events have not been available. In this multi-year research project we focused on developing and evaluating two potentially field-deployable methodologies: (1) monitoring temporal patterns of excreted steroid hormones as a tool to verify exposure and modulation of normal hormone levels, and (2) use of miniaturized, time-lapse, remote videography for acquiring nesting behavior and productivity data that could be used to quantify effects on free-ranging birds. Methods were first validated in a laboratory setting, using a breeding colony we established from wild-caught house finches (Carpodacus mexicanus). During 2000 and 2001, fecal-urate-urine (FUU) samples were collected at regular intervals during the mating and nesting season while behaviors of finches were monitored around-the-clock via time-lapse videography. In 2000, females were subcutaneously implanted with time-release 17b estradiol or placebo tablets at the time birds were paired. In 2001, this process was repeated with males similarly exposed to 17b estradiol, as male courtship and nest building behaviors also may be altered by estrogen. Estrogen and androgen levels in the FUU samples were quantified using a competitive-binding enzyme immunoassay (EIA) in 2001 and by radio immunoassay (RMA) in 2002. Reproductive and social behaviors of 16 and 18 pairs of males and females were quantified from the videotapes in 2001 and 2003, respectively. Temporal patterns of estrogen and androgen excretion were correlated with behavioral data to evaluate the hypotheses that excreted hormone levels (1) reflect circulating levels and (2) correlate with reproductive behavior, e.g., carrying nest material, nest construction, egg laying and incubation. Excreted estrogen and androgen correlated positively with nest construction and negatively with incubation.

In 2002, we brought the methods to the field and evaluated their applicability with free-ranging songbirds and California quail (Callipepla californica). Several uniquely designed feeding stations equipped with digital video equipment and feces collection devices were deployed for repeated collections of FUU samples from local populations of songbirds. Mist netting was conducted at the feeding stations to capture and implant time-release estradiol tablets in a portion of the local birds. Implanted birds were color-marked on the head for identification on video and subsequent separation of FUU samples from treated verses non-treated birds that visited the feeding stations. California quail were captured, implanted with time-release estradiol or placebo tablets and equipped with radio transmitters. Thereafter they were relocated repeatedly at night roost sites where FUU samples were collected at regular intervals until females began incubating eggs. Video equipment was established at nest sites and reproductive success data were collected. FUU samples of songbirds and quail were analyzed via RIA to verify that estrogen-exposed birds could be identified in free-ranging populations. The video data will be used to quantify behaviors and productivity variables. These studies demonstrated that effects resulting from exposure of birds to exogenous estrogen (and, by extension, from other endocrinologically active substances in the environment) can be detected in the field via FUU analysis and remote videography.
Biography
Larry Brewer has been studying birds for over 30 years, concentrating on avian toxicology for the last 20. After 15 years as a research biologist for the Washington State Department of Wildlife, in 1983, he was assigned to a time-share arrangement between that Department and Western Washington University where he was to assist in developing the Institute of Wildlife Toxicology. In just a matter of about 36 months, that became a full time endeavor, and it has been non-stop wildlife toxicology ever since. In 1989 he joined the faculty at Clemson University in the Department of Environmental Toxicology where he was among the small group of scientists that initiated The Institute of Wildlife and Environmental Toxicology (TIWET) in which he served as the Ecotoxicology Research Section Leader. In 1993 he resigned from academia to embrace the world of private consulting and research in the ecotoxicology field. He joined Springborn Smithers Laboratories as Director of Avian Toxicology in 2001 and that is the platform from which he has been participating in ACC’s Long-Range Research Initiative.
Panel Member Biographies

Dr. Matti J. Jantunen, KTL Department of Environmental Health, Finland

Matti Jantunen is a founding member of ISIAQ (vice President for Policy, 2000-2003), and a member of ISEA (President 2000-2001), A&WMA, AAAS and Σθ. He coordinated the ECA (European Coordinated Action) “Air Pollution Epidemiology” (1990-95) and serves on the Steering Committee of the ECA “Urban Air, Indoor Environment and Human Exposure.” He has also served WHO in numerous working groups (e.g. Air Quality Guidelines for Europe), and chaired WHO Task Force for Human Exposure Assessment (Kyoto - Montreaux 1996-98). He has co-chaired numerous International Conferences, including the Indoor Air 1993 in Helsinki, ISEE-ISEA 1999 in Athens, Healthy Buildings 2000 in Helsinki and ISEA 2003 in Stresa, Italy.

Jantunen received his MSME 1972 at Tampere University of Technology and MSEE 1976 and PhD 1978 at the University of North Carolina/Chapel Hill SPH. In the ’80's he worked on power plant emissions, organic mutagens, Chernobyl fallout and indoor air quality. Since ’90 he has focused on air pollution exposure. He coordinates the European EXPOLIS study, which has expanded to new topics, such as exposure modelling, source apportionment and risk analysis. He has authored and co-authored 126 international scientific articles and reviews.

His permanent position is research professor at the KTL Department of Environmental Health in Kuopio, Finland, but from 1999 to 2001 he served as a visiting scientist in EC JRC, Ispra, Italy.

Dr. Mary Kay O’Rourke, The University of Arizona

Mary Kay O’Rourke is an Associate Professor of Public Health Research and a Research Associate Professor in Medicine at The University of Arizona. She participates in both the Environmental and Occupational Health & Epidemiology Units of the College of Public Health. She has conducted interdisciplinary environmental research for over 20 years. She has been a Principal Investigator or a Co-Principal Investigator on several exposure assessment surveys investigating metal, pesticide, VOC and PAH exposures. These studies include the National Human Exposure Assessment Survey, the Arizona Board Survey, two surveys examining pesticide exposure among children in Yuma County Arizona and a pesticide exposure in the Gila River Indian Community. She has extensive experience in designing and implementing exposure assessment field surveys, quality assurance programs and the data processing protocols for large studies. She is also a member of the Respiratory Sciences Center where she evaluates human symptom response to bioaerosols (pollen, mold, house dust mites) using the tools of exposure assessment. She has been recognized for her work with bioaerosols as an honorary member of the Arizona Allergy Society and internationally as an elected member of the International Academy of Indoor Air Sciences. Her work in the College of Public Health has been recognized through induction into Delta Omega.

Dr. Chris Saint, U.S. Environmental Protection Agency

Chris Saint is currently the Assistant Center Director in EPA’s National Center for Environmental Research. In this position, he is responsible for all research planning and implementation activities conducted by the Center on issues concerning pesticides and other toxic chemicals. This includes human exposure, effects in sensitive populations such as children, aggregate and cumulative risk, toxicology, human variability, endocrine disruption, and sociological research to support risk assessment. During his 17 years with the
EPA, Dr. Saint has coordinated and worked with exposure monitoring, risk assessments, and policies related to human exposure to toxic chemicals. He also managed a nation-wide research program investigating the effects of acid deposition on ecological resources. Dr. Saint holds degrees in chemistry and biochemistry from Loughborough University in the United Kingdom.

Dr. Germaine Buck, National Institute of Child Health and Human Development

Germaine M. Buck is a reproductive and perinatal epidemiologist with particular interest in the relation between environmental agents and human reproduction and development. Dr. Buck was formerly a professor in the Department of Social & Preventive Medicine, University at Buffalo, and is currently Chief of the Epidemiology Branch, Division of Epidemiology, Statistics and Prevention Research, National Institute of Child Health & Human Development, National Institutes of Health, Department of Health & Human Services. She is a member of the ACC’s Epidemiology Technical Implementation Panel, past member of the Committee of Toxicology, National Research Council and Past-President of the Society for Pediatric & Perinatal Epidemiologic Research.

Dr. Thomas E. McKone, Univ. of California, Berkeley/Lawrence Berkeley National Lab.

Biography previously provided on page 29.

Dr. Linda Sheldon, U.S. Environmental Protection Agency

Biography previously provided on page 30.

Dr. Halûk Özkaynak, U.S. Environmental Protection Agency

Biography previously provided on page 32.

Dr. Larry L. Needham, Centers for Disease Control and Prevention

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Dr. Fred Miller, CITT Centers for Health Research

Biography previously provided on page 35.
Improved Methods:
Toxicity Test Methods Emphasizing Development

1 Developmental Immunotoxicity of Dexamethasone in the Rat: Comparison of Fetal vs. Adult Exposure

R.R. Dietert and J. Lee

Department of Microbiology and Immunology, College of Veterinary Medicine, Cornell University, Ithaca, NY

Dexamethasone-21 phosphate (DEX) was administered (s.c.) to pregnant CD-1 rats on days 6-21 of gestation (0, 0.0625, 0.125, 0.25, 0.5 mg/kg/day) with identical exposure of non-pregnant adult females. Some reproductive (ano-genital distance) and growth (body weight) measures were altered. In the juvenile (5 wk.), the delayed type hypersensitivity response to KLH was significantly reduced at all doses examined and this pattern continued into adulthood (13 wk.). In contrast, the DTH response of adults exposed to DEX was unaltered even at the highest dose. Few DEX-induced changes were seen in offspring or adult blood parameters or in splenocytes analyzed for cell surface markers (by flow cytometry). In contrast, the thymus of both exposed pups (both ages) and adults showed a marked reduction in cortex area beginning with the 0.125 mg/kg/day DEX exposure level. Macrophage production of TNF and NO was only marginally affected, as was splenocyte production of IL-4 and IFN gamma. In contrast, pups assessed as juveniles were significantly depressed in splenic IL-2 production with changes also evident for IL-10. DEX exposure altered serum antibody levels across age groups with KLH-specific IgG being elevated (beginning with the 0.0125 dose) while total IgE was reduced. These results suggest that while DEX exposure produces some common alterations following in utero vs. adult exposure, fetal exposure (even at the lowest doses tested) produces marked and persistent functional loss (DTH) not evident in exposed adults. Furthermore, there was no apparent advantage in delaying assessment to adulthood.
Improved Methods:
Toxicity Test Methods Emphasizing Development

2 Pathologic and Immunologic Responses in the Respiratory Tract of A/J Mice after Intranasal Sensitization and Challenge with Trimellitic Anhydride

A. Farraj, J.R. Harkema, and N.E. Kaminski

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Sensitization of the respiratory tract to low molecular weight chemicals (LMWC) including trimellitic anhydride (TMA) is a leading cause of occupational asthma and allergic rhinitis in industrial settings. Mucus hypersecretion and airway inflammation consisting of lymphocytes and eosinophils are pathologic features of such allergic airway diseases (AAD). Many experimental models have linked LMWC-induced AAD to Th2 cytokine expression. Most murine models, however, use systemic administration (e.g., topical) to sensitize mice. The present study tests the hypothesis that intranasal sensitization and challenge with TMA will induce the immunologic and pathologic responses characteristic of LMWC-induced AAD in the nasal and pulmonary airways. A/J mice were intranasally sensitized and then intranasally challenged twice with TMA or 1:4 ethyl acetate/olive oil vehicle. Nasal and pulmonary airways were processed for light microscopic examination. Nasal airways and right lung lobes were analyzed for Th2 cytokine mRNA expression using real-time PCR and total serum IgE was measured using an ELISA. Only mice that were intranasally sensitized and challenged with TMA had a marked allergic rhinitis characterized by an influx of eosinophils, lymphocytes and plasma cells, 24 h after the final challenge. By 96 h, the nasal airway epithelium exhibited increases in stored mucus and a regenerative hyperplasia. Only TMA-sensitized and challenged mice exhibited an increase in nasal airway-derived IL-4, IL-5, and IL-13 expression. In addition, only TMA-sensitized and challenged mice exhibited an increase in lung-derived IL-5 mRNA and elevated total serum IgE that was 4-fold the control level by 24 h after exposure and persisted at that level by 96 h. However, no pulmonary lesions were found in any group. This study is the first to demonstrate that intranasal administration of a LMWC is an effective method of sensitization resulting in the hallmark features of allergic rhinitis and the up-regulation of critical mediators of AAD, IL-4, IL-5, and IL-13 within the nose, IL-5 within the lung, and total serum IgE after challenge.
Improved Methods:
Toxicity Test Methods Emphasizing Development

3 Can Non-Invasive Plethysmography Predict Respiratory Allergy to Chemicals?

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Non-invasive plethysmography in mice is being evaluated for use in predicting the potential of chemicals to cause respiratory allergy. This technique measures enhanced pause (Penh), an index of airway hyperresponsiveness (AHR), which is a characteristic pathophysiologic outcome in asthma. To determine the utility of non-invasive plethysmography as a predictor of respiratory allergy, toluene diisocyanate (TDI) and trimellitic anhydride (TMA) were used as prototypical respiratory sensitizers, while the well-known skin sensitizer, DNCB, was employed as a negative control.

Results: The vehicles used to deliver sensitizers into the lungs of mice by intranasal insufflation were without effect on AHR or pulmonary inflammation, neither were sensitizers delivered into normal (unsensitized) mice. Also, after skin sensitization with DNCB, respiratory challenge had no effect on AHR or lung inflammation. TDI, but not TMA, did cause increased airway responsiveness (AHR) when administered to skin-sensitized mice. Both molecules increased the Penh baseline. No increase in lung inflammation was observed with these treatments.

Conclusion: Identification of respiratory sensitizers by non-invasive plethysmography under the tested conditions is not satisfactory.
Improved Methods:
Toxicity Test Methods Emphasizing Development

4 Determination of the Potential Susceptibility of the Developing Immune System of the Rat to Immunosuppression by the Pesticide Heptachlor

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A panel of in vivo, ex vivo and in vitro assays were employed to determine whether the developing (i.e., early gestation to pre-puberty) rat immune system exhibits increased susceptibility to immunosuppression by heptachlor (HE) compared to young adults. Dams were dosed from gestational day 6 (GD6) through post-natal day 21 (PND21), at which time the pups were weaned and dosed directly until PND42. Young adult rats (6-weeks-old) were dosed for 3 weeks. HE was administered in corn oil by gavage at 0, 0.03, 0.1, 0.3, 1.0 and 3.0 mg/kg/d. Male and female rats were tested for the delayed type hypersensitivity (DTH) response, phagocytic activity of macrophages, splenic natural killer (NK) cell activity, phenotypic analysis of splenic and thymic cells, and antibody response to sheep red blood cells (SRBCs). Exposure to HE, either during immune system development or early adulthood, did not alter body, spleen or thymus weights, NK cell activity, DTH response, IgM or IgG anti-SRBC response, or macrophage phagocytosis in either males or females. Phenotypic analysis of splenic CD5⁺ (pan T cells), CD4⁺ (helper T cells), CD8⁺ (cytotoxic T cells) and CD161⁺ (NK cells), and thymic CD4⁺ cells indicated no alteration in these cells compared to controls. However, percentages of thymic CD5⁺ cells, in rats exposed during immune development, were suppressed at 1.0 and 3.0, and at 3.0 mg HE/kg/d in males and females, respectively. In young adult rats, the percentage of thymic CD5⁺ cells was also suppressed at 3.0 mg HE/kg/d in males and at 0.3 -3.0 mg HE/kg/d in females. A decrease was observed in CD4⁺/CD8⁺ thymic cells at 3.0 mg HE/kg/d in females, and at 1.0, and 3.0 mg HE/kg/d in males exposed during immune development. Furthermore, in adult exposed rats the percentage of CD4⁺/CD8⁺ thymic cells was decreased at 1.0 and 3.0, and at 3.0 mg HE/kg/d, in males and females respectively. Unfortunately, these changes in the proportions of different T cell sub-sets cannot be linked to alterations in immune function since HE affected none of these functions. (This abstract does not reflect EPA policy. Supported in part by the American Chemistry Council.)
5 Cellular and Molecular Targets During Androgen-Mediated Male Reproductive Tract Development

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The objectives of this project are to (1) identify key cellular and molecular processes during male rat reproductive tract development in utero that are targets for endocrine-active chemicals and (2) link these altered processes with adverse response. Previously, we examined global changes in gene expression in the developing rat testis following in utero exposure to di(n-butyl) phthalate (DBP), a chemical that causes antiandrogenic effects on the developing male rat reproductive tract. Our gene expression data indicate that the antiandrogenic effects of DBP may be the result of decreased expression of multiple genes in the steroidogenic pathway. DBP-induced alterations in gene expression were distinct from but overlapped with alterations in gene expression induced by flutamide. Based on these preliminary data, we anticipate that we can characterize the molecular mechanisms of action of structurally diverse antiandrogens. We hypothesize that exposure to structurally diverse endocrine-active chemicals during critical windows of development will cause both unique and common cellular and molecular alterations that are related to mechanism of action and indicative of adverse response. This hypothesis will be tested by investigating the following specific aims. (1) Determine the cellular and molecular mechanisms by which developmentally toxic phthalate esters reduce fetal testicular testosterone synthesis and link reduced testicular testosterone with testicular and epididymal malformations. (2) Identify cellular and molecular targets of competitive androgen receptor antagonists in the developing male rat reproductive tract and link androgen receptor antagonism with testicular and epididymal malformations. (3) Determine the consequences on the developing male rat reproductive tract of exposure to combinations of mechanistically diverse antiandrogens. Results from this study will be combined with tissue dosimetry data to develop predictive models for the effects of antiandrogens on rat male reproductive development. Together with knowledge of human male reproductive development in utero, this information will be essential in determining the relevance of the in utero male rat model for assessing human risk.
Improved Methods:
Integration and Implications of New and Emerging Approaches in Health Effects Research

6 Binary Mixtures of Organophosphates: Experimental Data and Predictive Modeling
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This project investigated: in vitro inhibition and predictive modeling of brain (target) or serum (protective) cholinesterases by mixtures of oxons of organophosphorus insecticides; in vitro inhibition of the liver or serum carboxylesterases; involvement of the catalytic A-esterases in detoxication of oxons in liver or serum in vitro; and in vivo patterns of cholinesterase and carboxylesterase inhibition following exposure to insecticide mixtures. Exposures to the compounds were either simultaneous or sequential. For the inhibition of cholinesterase from oxon mixtures, mass action models using ordinary differential equations predicted the inhibition in brain homogenates. In investigations of detoxication with mixtures of oxons, oxon detoxication correlated reasonably well with carboxylesterase inhibition, suggesting that stoichiometric detoxication by carboxylesterases was responsible for the majority of the detoxication observed in serum, while in liver an additional mechanism is operating on the dimethyl oxons. Only chlorpyrifos-oxon and diazoxon were substrates for A-esterases at low oxon concentrations. In the in vivo studies, mixtures of azinphosmethyl and parathion, whether administered simultaneously or sequentially, yielded apparently additive effects on brain cholinesterase, with no indication of interactions between the compounds. However, while chlorpyrifos and methyl parathion mixtures yielded apparently additive effects on brain cholinesterase inhibition when administered simultaneously, these two compounds administered sequentially yielded a greater than additive effect. Predicting effects of mixtures in vivo will require a knowledge of both activation and detoxication potentials, potencies of the oxons as cholinesterase and carboxylesterase inhibitors, ability of the oxons to serve as substrates for A-esterases, and time sequence of exposure to the compounds.
Improved Methods:
Integration and Implications of New and Emerging
Approaches in Health Effects Research

7 Designs and Strategy for Tests of Gene Environment Interaction
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Case-only, partial case-control, and case-parent trio design have been advocated as alternatives to the conventional case-control design to test for gene-by-environment (GxE) interactions. These methods are attractive, as they require much less information and/or genotyping efforts. Further, case-only and partial case-control designs can be more powerful than case-control for tests of GxE interaction. However, these designs are only valid when an assumption of independence between genetic and environmental risk factors in the general population can be met. It is still unclear to what extent one design may be more powerful for detecting GxE interaction and/or more robust to violation of the independence assumption. We have designed a Monte Carlo simulation strategy to compare false positive rates (FPR) and statistical power to detect GxE interaction across these four designs under various interaction scenarios. We show the expected increase in FPR as the GxE independence assumption is violated for all designs, except the complete case-control design. When the independence assumption is met, however, the case-only and partial case-control designs do provide greater statistical power for tests of interaction.

One strategy for incorporating these results may be to use the powerful case-only design to screen for GxE interactions, followed by an unbiased case-control analysis of promising interactions. With the advent of high-throughput single nucleotide polymorphism (SNP) genotyping, a two-stage strategy using haplotypes could provide an efficient way for data reduction, and could be used to analyze genome-wide information to identify regions or candidate genes that modify exposure or treatment effects on disease outcomes.

This work was supported by a grant from the American Chemistry Council awarded to Dr. Fallin.
Improved Methods:  
Integration and Implications of New and Emerging 
Approaches in Health Effects Research

8  The National Environmental Respiratory Center: Disentangling the Health Effects of Complex Mixtures of Air Contaminants

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Our current implementation of the Clean Air Act focuses largely on a limited number of pollutants, pollutant classes, and sources that tend to be reviewed, debated, and studied one-at-a-time in a "revolving door" manner. Although Section 103 of the Act clearly mandates consideration of combinations of air pollutants, our single-pollutant, single-source regulatory-research cycle has left us with poor ability to put the contributions of different natural and man-made air contaminants, their combinations, and their sources into context. Of course, people always breathe complex, variable mixtures of air contaminants. We need new research strategies if we are to substantially refine our understanding of the air quality-health relationship. The National Environmental Respiratory Center (NERC) was initiated by Congress as a government-industry collaborative effort to improve our understanding of the contributions of individual pollutant species and combinations contained in common source emissions to the cardio-respiratory health effects associated statistically with air pollution. The program is funded to date by the U.S. Environmental Protection Agency as the lead agency, four other federal and state agencies, and sixteen non-federal entities, including the American Chemistry Council. In short, the NERC strategy is to create, and then analyze, a detailed exposure-dose-health response database created by conducting identically-designed inhalation studies of source emissions of regulatory interest. The exposures, comprising complex mixtures of different but overlapping composition, are being analyzed in greater detail than in previous toxicology studies. The protocol includes four concentrations, all within a plausible human exposure range (plus negative control). The first four exposures include contemporary "on-road" diesel emissions, "on-road" gasoline emissions, hardwood smoke, and downwind coal combustion emissions. Health responses are evaluated by a range of models encompassing five general categories of response: inflammation/cytotoxicity, development and exacerbation of respiratory allergic immune responses, resistance to respiratory bacterial and viral infection, respiratory and cardiac function, and cancer. Each source emission study adds a "layer" to the exposure-response database, which will be analyzed to reveal the individual physical-chemical species, and combinations of species, driving the different health effects. The work will also provide useful direct comparisons among common source emissions. The diesel emissions and hardwood smoke exposures are completed, preparations are underway for the gasoline emission exposure, and plans are being developed for the coal emissions exposure. The poster will review the program's strategy, status, and key findings to date.
Airborne particles are a widespread environmental health concern. They are known to induce a variety of important lung diseases and possibly exert significant nonpulmonary systemic effects. Much experimental work has demonstrated that the physicochemical properties of particles are in large part responsible for their pathologic potential, and there has been recent interest in the role of the ultrafine particulate fraction (< 0.1 mm diameter) in the generation of adverse effects. We intend to compare global gene expression using a cDNA microarray approach in lungs and hearts of rats following exposure to both ultrafine particles and fine-mode particles (0.1–1.0 mm diameter) to determine whether ultrafine particles impart a separate response spectrum than do larger particles. We hypothesize that there are important physicochemical properties of particles that will lead to signature profiles of gene expression predictive of adverse lung outcomes. Another objective of the present studies is to compare and contrast pulmonary gene expression in rats that inhale toxic fibrogenic particles versus those that inhale poorly soluble, persistent (PSP), low-toxicity particles. We will compare pulmonary gene expression between rats exposed to high-toxicity particles versus those exposed to PSPs at concentrations that impair alveolar-macrophage-mediated lung clearance (so-called pulmonary overload) and lead to fibroproliferative lung disease. Because particle lung toxicity studies to date have focused on cell proliferation, inflammation, extracellular matrix, and oxidant-induced injury, we will focus on important genes that mediate steps in these pathways as we analyze cDNA array data.
Improved Methods:
Methods to Detect Effects on Wildlife

10 Investigation of Chemical Mixtures in the Upper Ocklawaha River Basin: Reproduction, Development, and Endocrine Status in Alligators, Fish, and Mussels

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Specific aims of this project include (1) development and validation of assays for endocrine sensitive endpoints in alligators, fish, and freshwater mussels for use in interaction and whole mixture studies; (2) determination of an appropriate combined action model for predicting the effects of binary and ternary mixtures of endocrine-active compounds; and (3) testing the utility of binary interactions for predicting the toxicity of more complex mixtures found in the Ocklawaha River Basin in Florida where putative endocrine disruptive effects have been reported. Assays were developed for vitellogenin, an estrogen-sensitive protein, in alligators, largemouth bass, and mussels. Exposure of the freshwater mussel Elliptio buccleyi to estradiol produced an increase in circulating estradiol and vitellogenin. Differences were observed in the SDS-PAGE banding patterns of vitellogenin in alligators from control versus contaminated sites. Responses of bass and mussels to \( p,p' \)-DDE and dieldrin, two major contaminants in the Ocklawaha system, were characterized in preparation for binary mixture studies. Several endocrine-relevant endpoints were affected in bass, including a significant dose-dependent decrease in circulating estradiol. Analysis of the data from mussels is underway. Current work is focused on characterizing the dose-response of alligator neonates to DDE and dieldrin, characterizing differences in vitellogenin metabolites in adult alligators, and initiation of binary and ternary mixture studies in mussels and largemouth bass. Future research will use the results of the binary interaction studies in a combined action model to predict the effects of defined, more complex mixtures on endocrine-sensitive endpoints in these three animal models.
Improved Methods:
Methods to Detect Effects on Wildlife

11 Development and Verification of Field-Deployable Methods for Evaluating Exposure and Effects of Endocrine-Active Substances in Wild Bird Populations

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There is a general concern that low amounts of pervasive chemicals in the environment may be affecting songbirds through estrogenic effects, thus changing their mating behaviors and reproductive output. However, methods for monitoring and/or detecting such events have not been available. In this multi-year research project we focused on developing and evaluating two potentially field-deployable methodologies: (1) monitoring temporal patterns of excreted steroid hormones as a tool to verify exposure and modulation of normal hormone levels, and (2) use of miniaturized, time-lapse, remote videography for acquiring nesting behavior and productivity data that could be used to quantify effects on free ranging birds. Methods were first validated in a laboratory setting, using a breeding colony we established from wild-caught house finches (Carpodacus mexicanus). During 2000 and 2001, fecal-urate-urine (FUU) samples were collected at regular intervals during the mating and nesting season while behaviors of finches were monitored around-the-clock via time-lapse videography. In 2000, females were subcutaneously implanted with time-release 17β estradiol or placebo tablets at the time birds were paired. In 2001, this process was repeated with males similarly exposed to 17β estradiol, as male courtship and nest-building behaviors also may be altered by estrogen. Estrogen and androgen levels in the FUU samples were quantified using a competitive-binding enzyme immunoassay (EIA) in 2001 and by radio immunoassay (RIA) in 2002. Reproductive and social behaviors of 16 and 18 pairs of males and females were quantified from the videotapes in 2001 and 2003, respectively. Temporal patterns of estrogen and androgen excretion were correlated with behavioral data to evaluate the hypotheses that excreted hormone levels (1) reflect circulating levels and (2) correlate with reproductive behavior, e.g. carrying nest material, nest construction, egg laying and incubation. Excreted estrogen and androgen correlated positively with nest construction and negatively with incubation.

In 2002, we brought the methods to the field and evaluated their applicability with free-ranging songbirds and California quail (Callipepla calliflorna). Several uniquely designed feeding stations equipped with digital video equipment and feces collection devices were deployed for repeated collections of FUU samples from local populations of songbirds. Mist netting was conducted at the feeding stations to capture and implant time-release estradiol tablets in a portion of the local birds. Implanted birds were color-marked on the head for identification on video and subsequent separation of FUU samples from treated versus non-treated birds that visited the feeding stations. California quail were captured, implanted with time-release estradiol or placebo tablets and equipped with radio transmitters. Thereafter, they were relocated repeatedly at night roost sites where FUU samples were collected at regular intervals until females began incubating eggs. Video equipment was established at nest sites and reproductive success data were collected. FUU samples of songbirds and quail were analyzed via RIA to verify that estrogen-exposed birds could be identified in free-ranging populations. The video data will be used to quantify behaviors and productivity variables. These studies demonstrated that effects resulting from exposure of birds to exogenous estrogen (and, by extension, from other endocrinologically active substances in the environment) can be detected in the field via FUU analysis and remote videography.
Improved Methods: 
Methods to Detect Effects on Wildlife 

12 Evaluating Habitat Use to Improve Exposure Assessment in Ecological Risk Assessments 
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Environmental management decisions often rely on ecological risk assessments. Too often, risk estimates fail to consider critical landscape features, which define wildlife use patterns. Conceptual exposure models often are based on overly simplified assumptions of ecological relationships. The consequences of the simplifying assumptions can greatly overestimate the risk to some species and greatly underestimate the risk to others. We have developed procedures to integrate landscape features, which define habitat quality as key modifiers of exposure estimates. Our approach guides: (a) selection of assessment species, keyed to wildlife distribution ranges, species habitat requirements, and exposure assessment parameters; (b) data collection for reconnaissance-, screening-, and definitive-level assessments; (c) generation of spatially explicit descriptions of habitat quality for assessment species; and (d) allocation of exposure estimates using both habitat quality and spatial variations in chemical concentration. This can guide planning processes so that assessments consider the most relevant species of the area, define which parameters to measure, and result in more realistic exposure assessments. The approach expands the range of available site management options. For example, habitat enhancement may be used to draw animals away from contaminated zones. Contaminated localities that also have poor quality habitat may be treated with less costly methods (e.g., bioremediation). Finally, direct comparisons of lost resources stemming from intrusive remediation options, which often destroy valuable wildlife habitat can be factored into the decision process. 

Information from approximately 90 Habitat Suitability Index (HSI) models has been abstracted into an ACCESS® Database and EXCEL® Workbooks. This information includes description of all variables required to calculate HSI values, areas of applicability, qualitative sensitivity analyses, and suggested methods available to obtain field data. The EXCEL® Workbooks contain executable equations for each of the models, which convert the raw data from each variable into the corresponding HSI value. 

This work will be related to a recent symposium by the American Society for Testing and Materials (ASTM) E47 Committee (Biological Effects and Environmental Fate) on Landscape Ecology and Wildlife Habitat Evaluation. Comments on the future implementation of the approach will also be presented.
13 Effects of A Synthetic Estrogen on Aquatic Populations: A Whole Ecosystem Study

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A whole-lake experiment was conducted at the Experimental Lakes Area in northwestern Ontario to determine whether the potent synthetic estrogen ethynylestradiol (EE2) adversely affects aquatic populations. As part of a larger ecosystem-level study, bacterial, algal, zooplankton, amphibian and benthic invertebrate populations were characterized in the experimental and reference lakes in 1999 and 2000, and monitored during continuous EE2 amendments (mean concentration of 6.1 and 5.0 ng/L) in the summers of 2001 and 2002. In the treatment years, bacterial concentrations and growth rates in the experimental lake were similar to pre-addition data and to the reference lakes. Algal concentrations were also similar in all 4 years but community diversity was lower during both years of EE2 additions. While zooplankton abundances were not impacted, some species had reduced numbers of eggs and fewer males in the study lake in 2001 and 2002. Abundances of rotifers were also lower in the treatment years as compared to pre-addition data. Leech community composition, abundance, and growth of individual species did not differ across years in the treated lake, and no effects were observed on the mass or sizes of reproductive organs. Community composition of larval benthic invertebrates was not affected by EE2 exposure, but the timing of male and female chironomid emergence was impacted during the first year of treatments. Growth and development of caged mink and green frog tadpoles were not affected by EE2 exposure; however, low incidence of intersex was observed in both the wild and caged tadpoles from the treated lake. These results suggest that low concentrations of a potent estrogen agonist can have effects upon the populations of some lower-trophic-level biota.

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Improved Methods:
Methods to Detect Effects on Wildlife

14 EXPECT: EXtrapolation Practice for Ecological effeCT characterization of chemicals

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Recognizing the need to determine of the state of extrapolation practice for ecological effects characterization of chemicals and suggest improvements in the process, the project goal is to prepare a wide-ranging compilation of procedures for extrapolation of ecological risks which will include the data required and the methods themselves. Several relevant data sets for several key model substances and mixtures will be prepared for use as examples of extrapolation methods and to stimulate critical assessment of the extrapolation procedures at a stakeholder workshop. Using participation from international experts in risk assessment from regulatory agencies, academia, and industry, the workshop will gather feedback on the utility of proposed methods, suggest new or modified ones, and run case-study substances through the extrapolation procedures. The experience gained at the workshop will be incorporated into deliverables for dissemination of the information through conference presentations and publication of the report as a book, strongly based in science, but offering practical guidance to users and managers. The research process will utilize the expert panel approach and Delphi techniques with stakeholders to combine and prioritize ideas and approaches into a final usable format. The techniques developed in this research are expected to have significant impacts on current approaches to assessing risk of anthropogenic substances in the environment. The research will address the key question how best to extrapolate from single-species laboratory toxicity data to responses in the ecosystem. These techniques will be useable by scientists, regulators and the public to more effectively and efficiently protect the environment.
Improved Methods:  
Methods to Detect Effects on Wildlife

15 Evaluation of Fence Lizard Eggs as a Reptile-Egg Screening Assay for Endocrine Disrupting Chemicals

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Relatively few laboratory studies have been conducted on the effects of endocrine disrupting chemicals on reptiles and no standardized test involving reptile models exists. Some wild populations of reptiles are affected by endocrine disrupting chemicals in contaminated habitat. In addition, laboratory studies have demonstrated that estrogenic chemicals can affect sex determination of reptiles whose sex is determined by incubation temperature. However, the effects of endocrine disrupting chemicals on reptiles with genotypic sex determination are unknown. Fence lizards (Sceloporus spp.) have genotypic sex determination and have two types of secondary sex characteristics. The first consists of enlarged post-anal scales that develop in male embryos and the second type consists of sexually distinct coloration that develops in subadult males. The purpose of our research was to evaluate the sensitivity of post-anal scale development to an estrogenic chemical (17α-ethinylestradiol). We examined the dose-related effects of in ovo exposure to ethinylestradiol in western fence lizards, Sceloporus occidentalis. Lizard eggs were microinjected with amounts of ethinylestradiol that ranged from 1 to 0.000001 µg per egg. We observed a dose response to ethinylestradiol relative to hatching success and development of post-anal scales. Development of post-anal scales in fence lizard embryos is a sensitive endpoint that can be used to test endocrine disrupting chemicals.
Improved Methods:
Methods for Characterizing and Estimating Exposures

16 A Comprehensive Chemical Exposure Framework Based on a Nested Loop Approach and a Taxonomy of Longitudinal Change in Exposure Related Parameters

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Simulation models have been identified as the preferred tool for characterizing uncertainty and variability in longitudinal exposures to multiple sources by multiple routes of exposures. Construction of these models requires a conceptual design that separates and appropriately models the processes that determine uncertainty, inter- and intraindividual variability, as well as the process that determines the relationships between the various sources and doses received by the simulated individuals. A design is proposed to achieve these goals that is based on a series of four nested loops. The loops are, the exposure event loop that models the route-specific doses to one individual from each source at one point in time; the time step loop that moves an individual through time updating the sources and the individual’s characteristics, the variation loop that determines the initial characteristics of each individual modeled, and finally the uncertainty loop that characterizes the impact of uncertainties in the source to dose models and parameter values.

The time step loop requires data on how the exposure related parameters in an individual change over time. Obtaining data on these longitudinal changes presents a major challenge to simulation modeling since surveys of key factors (such as diet or time activity) are generally unable to track individuals over periods longer than a few days and typically do not include data on all of the parameters required to model all routes of exposure. This lack of data results in a need for longitudinal models of the exposure parameter values. A conceptual design is proposed for organizing data on parameters taken from multiple and independent surveys to construct internally consistent descriptions of the longitudinal variation in the parameter values for an individual. The design consists of a proposed taxonomy of longitudinal change and a method for using each type of change in longitudinal simulation models.
Improved Methods:
Methods for Characterizing and Estimating Exposures

17 Design of a Comprehensive Chemical Exposure Framework
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The Comprehensive Chemical Exposure Framework (CCEF) is a software-based system that allows disparate models and databases to seamlessly transfer information between one another. The purpose is to design an overarching framework that is comprehensive, modular, user-friendly, open-code, mass-conservative, and accurate. It needs to address multiple exposure routes, pathways, and durations, and account for probabilistic analyses, varying exposure duration, and dose-response. This design is unique in that it provides the industry model-developer a mechanism to link their science-support models with other models and databases without technical assistance from the framework developers. The design of the CCEF leverages concepts associated with existing frameworks and exposure-modeling methods that are in the forefront of the scientific community. The key to the CCEF will be the flexibility in its usability and ability to integrate and accommodate different exposure models (existing and future), required for American Chemistry Council and industry needs.

The CCEF is designed to provide an interface to visualize the problem; a mechanism to link more sophisticated, science-support models, when needed to explore more accurate and mechanistically based exposures and effects; for remote access of databases and models; for sensitivity/uncertainty analyses and parameter estimation; for linkages to Geographic Information Systems (GISs); a standard output visualization package; for unique models and datasets to communicate; for a user to prioritize information from multiple databases; backward compatibility with legacy codes; linkages to and utilization of other modeling frameworks (e.g., micro-environmental models); and the ability to address multiple types of contaminants, in addition to non-agricultural compounds.

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Improved Methods:  
Prediction of Target Tissue Dose  

18 Developing PBPK Models for Testosterone Dosimetry in the Perinatal Period in the Rat and Systems Biology Approaches to EAC Risk Assessment

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The proper development and function of male reproductive tract tissues depends on the presence of specific concentrations of androgens—testosterone (T) and dihydrotestosterone (DHT)—and androgen receptor (AR) at appropriate times. Endocrine disruption by antiandrogens occurs because these compounds inappropriately alter androgen-AR complex concentrations at various life stages. Assessment of the consequences of exposure to antiandrogenic compounds requires knowledge of androgen synthesis, distribution and elimination in various life stages, spanning periods from formation of reproductive tissues in utero through normal function of these tissues in the adult. This project integrates knowledge of the control of local and systemic androgen concentrations in the developing and adult male rat to produce a life-stage-inclusive pharmacokinetic (PK) model for the two primary endogenous androgens (T and DHT) in the rat. The initial organization of the PK model will rely on literature data already available for androgen kinetics, current PK and PBPK models developed for T, and targeted PK studies identified during model development. The resulting PK tools will assist in extrapolations of control of androgen-AR complex concentration over doses, dose routes and species, and improve methods for dose-response evaluations in human risk assessments for antiandrogenic xenobiotics.
Improved Methods: 
Prediction of Target Tissue Dose

19 Compound-Independent Dosimetry of Inhaled Material

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Risk assessments for respiratory toxicants are prone to specific uncertainties regarding inter- and intraspecies variability, high-to-low-dose extrapolation, and susceptible subpopulations. Computational modeling techniques using a system biology approach are particularly useful in reducing the uncertainties by identifying and studying various physical and biological parameters involved in the exposure-dose-response paradigm. The goal in this project is to develop methods to improve risk assessment from exposure to inhaled material rather than to state and test a particular hypothesis.

The major thrust of the project involves devising compound-independent, generic dosimetric models to predict gas uptake and particle deposition in the upper respiratory tract (URT) and lower respiratory tract (LRT) of humans and laboratory animals. Gas uptake and particle deposition in the URT are estimated by first reconstructing the airway geometry on the computer and numerically solving transport equations to track the fate of the inhaled gases and particles. Various mathematical models of particle deposition are generated for the LRT that are used to calculate site-specific and regional deposition. Extension of these models to cases of diseased lungs may help identify susceptible subpopulations. A second and complementary part of the project includes experimentally validating dosimetry models and providing a database on deposition of particles in laboratory animals for interspecies extrapolation. Mice and rats will be exposed to radiolabeled monodisperse particles in nose-only and whole-body exposure systems, and deposition in various locations of the lung will be measured. As part of this effort, research was initiated on the relative roles of methacholine challenge dosimetry and airway responsiveness in mouse strain responses. A third part of the project includes the evaluation and characterization of exposure environments for humans and laboratory animals. This includes studying various generation and exposure systems, characterizing exposure atmospheres, and evaluating various particle measurement devices.
Improved Methods:
Prediction of Target Tissue Dose

20 Transplacental Transfer of Genistein and Conjugated Metabolites in Sprague-Dawley Rats

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Genistein is a phytoestrogen present in soy and virtually all rodent diets. It has been reported to interact with estrogen receptors and shown to elicit estrogentic effects in developing rodents. The extent to which genistein and its metabolites are transferred across the placenta to the developing fetus is important to evaluate the actual dose of genistein associated with developmental effects. The objective of this study was to determine if genistein and its metabolites transfer across the placenta on gestation day 19 to the fetuses of pregnant Sprague-Dawley rats following an oral dose of 4 or 40 mg/kg genistein. At various time points following administration, rats were asphyxiated with CO₂ and blood taken from the dam and fetuses. The concentration of genistein and the major glucuronide (Gen-G) and sulfate (Gen-S) conjugates were quantitated in plasma by LC-MS/MS. The major metabolites in the maternal and fetal plasma were Gen-G and Gen-S, respectively, with a low concentration of genistein detected in both. These data suggest that the Gen-G may not be transported across the placenta as readily as genistein or Gen-S. Conjugation of genistein may also take place in the placenta and fetal liver and contribute to the concentration of these conjugates measured in fetal plasma. Since genistein, but not its conjugates, interact with the estrogen receptor, the level of genistein that is transferred to the developing fetus and remains unconjugated is critical in evaluating the exposure of this compound to the developing fetus.
21 Mechanisms of Olfactory Transport of Inhaled Metals

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Excessive accumulation of manganese or iron within the brain may lead to a loss of dopaminergic neurons and motor dysfunction. Some research on mechanisms involved in the transport of manganese and iron indicate that transferring plays a role in iron and manganese brain delivery, while other research indicates that brain manganese delivery is not transferring-dependent. Recent studies conducted by our laboratory have shown that olfactory transport is an important pathway by which inhaled manganese is initially distributed to the rat brain (Brenneman et al., 2000; Dorman et al., 2002). One goal of this project is to evaluate the olfactory transport of inhaled iron. Results from this experiment demonstrate that unlike manganese, iron does not undergo extensive olfactory transport following inhalation and that it is largely retained within the olfactory epithelium (OE). We have also shown that transferring co-localizes with iron suggesting that binding to this metal effectively sequesters this metal within the OE. Elucidation of the cellular mechanisms that determine why manganese, but not iron, is transported by the olfactory neuron may provide crucial insights into how these metals are delivered to the brain. Completion of these studies will dramatically improve our understanding of whether exposure to low levels of inhaled manganese or iron can result in elevated brain concentrations of these metals and thus increase the risk of human neurological disease.
22 Olfactory Toxicity of Hydrogen Sulfide

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Hydrogen sulfide (H$_2$S) is an important air pollutant produced by a variety of anthropogenic and natural processes associated with the decomposition of organic matter. Ambient air H$_2$S concentrations range from 0.1 to 4 ppb and this chemical is also produced endogenously by anaerobic bacteria in the mouth and gastrointestinal tract. Change in olfactory function is one of the more sensitive effects noted in humans following high-dose H$_2$S exposure. Studies conducted at CIIT have shown that sub-chronic inhalation exposure of male rats to $\geq$ 30 ppm H$_2$S (NOAEL = 10 ppm) results in widespread sensory neuron loss and basal cell hyperplasia in the olfactory mucosa (Brenneman et al., 2000a). We have recently demonstrated a positive correlation between the delivery of H$_2$S and the incidence of lesions within the olfactory epithelium (Moulin et al., 2002). This study relied on the use of a computational fluid dynamics (CFD) model to forecast regional H$_2$S flux within the rat nose. One goal of the current project is to extend our modeling efforts to apply a human nose CFD model to inhaled H$_2$S. A critical step in this process will be the completion of nasal uptake studies in rats to better estimate regional mass transfer coefficients used in conjunction with our CFD model. We will also compare lesion locations and regions of high H$_2$S flux predicted using a CFD model of mouse nasal passages. This effort will allow us to evaluate the validity of our hypothesis in a second animal species affected by H$_2$S inhalation. An improved understanding of factors, such as whether proton generation plays a role in the development of site-specific lesions within the rat olfactory epithelium, is also needed. This issue has broad toxicological relevance since similar olfactory lesions seen with H$_2$S exposure are observed following exposure to other weak acids. Thus, a second specific aim of this project is to determine whether altered tissue pH occurs in the rat olfactory epithelium following H$_2$S inhalation. This aim will build on efforts within the chlorine project and will test the hypothesis that nasal toxicity is mediated by pH changes. The studies proposed in this project should yield important new information that will allow for the development of an alternative RfC that more accurately considers regional delivery of this gas to the human nose.
Improved Methods:  
Prediction of Target Tissue Dose

23 Mechanisms of Adaptive and Adverse Responses in the Respiratory Tract Following Low-Level Exposure to Inhaled Reactive Gases: Dosimetry Modeling Core

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Interpreting endpoints from subchronic, low-level, animal exposure-response studies, such as epithelial changes and cytokine and genetic responses, in the context of adverse health effects is becoming increasingly important. To better understand mechanisms underlying such effects, CIIT has developed a Program integrating existing chlorine and hydrogen sulfide research with a dosimetry modeling core and a workshop ranking common rodent nasal responses to characterize effects as adverse and adaptive. In the dosimetry modeling core, computational fluid dynamics (CFD) models are used to predict regional nasal dosimetry for both chlorine and hydrogen sulfide. Core responsibilities include (1) constructing new CFD models based on the male and female B6C3F1 mouse, (2) mapping the location and extent of major epithelial types lining mouse and human nasal specimens, (3) conducting CFD simulations of inspired nasal airflow and inhaled chlorine and hydrogen sulfide uptake, and (4) confirming CFD model predictions by conducting experiments in hollow nasal molds. Initial efforts have focused on improving methods for obtaining digitized cross sections of male and female mouse noses that will be used to construct CFD models. Photographs of the cut block face of a slightly fixed, non-exsanguinated nasal specimen frozen in embedding media saturated with toner for contrast show the most promise to date. The CFD simulations resulting from this work will be integrated with laboratory experiments to study both dosimetry and toxicodynamics. This systems biology approach will provide information and context for the use of acute and low-level effects of chlorine and hydrogen sulfide in human health risk assessment.
Improved Methods:
Prediction of Target Tissue Dose

24 Modeling Inter-Individual Variation in Physiological Factors Used in PBPK Models of Humans

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Modeling interindividual variation in internal dose in humans using PBPK models requires data on the variation in the physiological parameters across the population of interest. These data must also capture the correlations between the values in each person. This project provides a source of data for human physiological parameters where (1) the parameter values for an individual are correlated with one another, and (2) values of parameters vary according to interindividual variation in the general population, by gender, race, and age. The parameters investigated in this project include: (1) volumes of selected organs and tissues; (2) blood flows for the organs and tissues; and (3) the total cardiac output under resting conditions and average daily inhalation rates. These parameters are expressed as records of values for the approximately 30,000 individuals evaluated in the NHANES III survey. A computer program (\textsuperscript{3}P\textsuperscript{3}M) is developed that allows records to be retrieved randomly from the database with specification of constraints on age, sex, and ethnicity. The database and accompanying software together provide a convenient tool for parameterization of human PBPK models of interindividual variation in pharmacokinetics.
Improved Methods:
Prediction of Target Tissue Dose

25 The Influence of Serum Binding Proteins and Clearance on the Comparative Receptor Binding Potency of Endocrine-Active Compounds

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One measure of the potency of compounds which lead to adverse effects through ligand dependent gene transcription is the relative affinity for the critical receptor. Endocrine-active compounds (EAC) that are presumed to act principally through binding to the estrogen receptor (ER), for example the isoflavone genistein, bisphenol A and octylphenol, is one such class of compounds. For purposes of making simple comparisons of potency, receptor-binding affinity has been equated to potency, which consequently defines the dose-response characteristics for the compound. Direct extrapolation of these \textit{in vitro} estimated potencies to the corresponding \textit{in vivo} system and to specific species or life-stages (neonatal, pregnant) can be misleading. Accurate comparison of the receptor-binding potency (RBP) of EACs requires characterization of biochemical and pharmacokinetic factors that affect the bioavailable concentration. Quantitative \textit{in vitro} and \textit{in vivo} models have been developed for integrating factors (serum protein and receptor-binding affinity, pharmacokinetics) that affect the relative binding potency of EACs. The approaches developed here provide a useful framework for utilizing experimental data from \textit{in vitro} and \textit{in vivo} studies to estimate the relative RBP of these compounds. Examples are presented to illustrate the utility of this model structure for integrating available information to conduct dose-response assessments of ER ligands (This abstract does not represent EPA policy).
Improved Methods:  
Prediction of Target Tissue Dose

26 Cellular and Molecular Targets during Androgen-Mediated Male Reproductive Tract Development

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The objectives of this project are to (1) identify key cellular and molecular processes during male rat reproductive tract development in utero that are targets for endocrine-active chemicals and (2) link these altered processes with adverse response. Previously, we examined global changes in gene expression in the developing rat testis following in utero exposure to di(n-butyl) phthalate (DBP), a chemical that causes antiandrogenic effects on the developing male rat reproductive tract. Our gene expression data indicate that the antiandrogenic effects of DBP may be the result of decreased expression of multiple genes in the steroidogenic pathway. DBP-induced alterations in gene expression were distinct from but overlapped with alterations in gene expression induced by flutamide. Based on these preliminary data, we anticipate that we can characterize the molecular mechanisms of action of structurally diverse antiandrogens. We hypothesize that exposure to structurally diverse endocrine-active chemicals during critical windows of development will cause both unique and common cellular and molecular alterations that are related to mechanism of action and indicative of adverse response. This hypothesis will be tested by investigating the following specific aims. (1) Determine the cellular and molecular mechanisms by which developmentally toxic phthalate esters reduce fetal testicular testosterone synthesis and link reduced testicular testosterone with testicular and epididymal malformations. (2) Identify cellular and molecular targets of competitive androgen receptor antagonists in the developing male rat reproductive tract and link androgen receptor antagonism with testicular and epididymal malformations. (3) Determine the consequences on the developing male rat reproductive tract of exposure to combinations of mechanistically diverse antiandrogens. Results from this study will be combined with tissue dosimetry data to develop predictive models for the effects of antiandrogens on rat male reproductive development. Together with knowledge of human male reproductive development in utero, this information will be essential in determining the relevance of the in utero male rat model for assessing human risk.
Improved Methods:
Understanding Toxicodynamics

27 Analysis of In Vitro/In Vivo Interactions in Endocrine-Active Mixtures

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Our studies utilized in vitro (MCF-7 cell ER-α reporter gene) and in vivo (rodent uterotrophic assay) models, in conjunction with novel statistical methodologies, to evaluate mixtures for endocrine-active chemicals. Initially, several mixtures containing well-characterized endocrine-active chemicals were used to verify the ability of our system to detect additive and non-additive (antagonism, synergy) responses. Using a full 4³ factorial (64 treatment groups) experimental design coupled with response surface statistical methodology, we confirmed the ability of the system to identify additivity (estradiol 17β[E2], DES, ethinyl estradiol[EE]), synergy (E2, EGF, IGF-I) and antagonism (E2, ICI 182,780), as expected. Additivity was also seen when the E2, DES, EE mixture was tested in the immature rodent uterotrophic model. However, high concentrations of this mixture revealed antagonism, demonstrating that interactions can be dose-dependent. Currently, we are studying interactions between phytoestrogens, which are present at high levels in human and animal diets, and synthetic estrogens, which tend to be present at low levels. In the rat uterotrophic assay, a mixture of o,p-DDT, methoxychlor, and β-hexachlorocyclohexane (each chemical present at 0.01 or 0.1X its individual NOEL) had no impact on the activity of phytoestrogens, while additivity was observed when each of the chemicals was present at 1X its individual NOEL. As environmental chemicals are generally present at levels well below their NOELs, a change in response from that due to phytoestrogen exposure would seem unlikely. We are currently studying potential interactions between phytoestrogens and mixtures of six synthetic estrogens for both tissue-level and molecular-level (gene expression) responses. Supported by the American Chemistry Council and The Dow Chemical Company.
Improved Methods:
Understanding Toxicodynamics

28 Dose-Response for Androgen-Receptor-Mediated Gene Expression

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Low-dose extrapolations may be either linear or nonlinear depending on the supporting database but in either case are typically assumed to be monotonic for risk assessment purposes. Data showing nonmonotonic dose-response curves exist but have not had a significant impact on risk assessment practices to date. This reflects uncertainties about the statistical significance of the nonmonotonic behaviors, about the distinction between adverse and nonadverse changes, and, most of all, about the biochemical mechanism giving rise to the behavior. This project will focus on the mechanism of a J-shaped dose-response behavior for androgen receptor- (AR) mediated gene expression in HepG2 cells elicited by hydroxyflutamide (O HF) or progesterone (P) in the presence of dihydrotestosterone (DHT). Computer simulation modeling will be used to explore the dose-response behaviors of plausible mechanisms that can be examined in the laboratory. Both genomic and nongenomic interactions of androgens will be studied. Genomic effects involve direct interactions of AR-ligand dimers with DNA. Nongenomic effects involve androgen interactions with the MAPK signal transduction pathway that in turn influence gene transcription. Studies of nongenomic interactions will initially be limited to computational analysis. Laboratory studies will use the HepG2-androgen receptor-luciferase reporter system with specialized assays, such as the chromatin immunoprecipitation (ChIP) assay, to characterize interactions of DHT and OHF or P with AR and with DNA leading to nonmonotonic dose-response relationships. The proposed studies will provide insights into the mechanism of the J-shaped dose-response behaviors seen experimentally. Follow-on work will examine the extent to which this behavior is found in alternative in vitro systems and in vivo. These studies will determine whether the J-shaped dose-response behaviors seen with OHF and P share a common mechanism and provide insight into the reasons for quantitative differences between the two dose-response curves. Subsequent research (not included in this proposal) could focus on the structural requirements for J-shaped dose-response behaviors. The long-range goals of this research are to understand the mechanistic determinants of J-shaped dose-response behavior for AR-mediated effects and the prevalence of such behaviors. Such information is needed before human health risk assessment can be expected to consider the possibility of J-shaped dose-response behaviors in the formal process of dose-response assessment for chemicals that interact with the AR.
Improved Methods:
Understanding Toxicodynamics

29 Cumulative Risk of Organophosphate Pesticides

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Organophosphate (OP) pesticides are a common-mechanism group that acts by inhibition of acetylcholinesterase (AChE). Exposure to several OPs at once is widespread, although at very low levels, since they occur as food residues, in drinking water, and in residences, schools, and commercial buildings. Recent federal legislation mandates assessment of the "cumulative risk" for such common-mechanism groups. The concern is that exposure to multiple members of a common-mechanism group might pose a health risk even if the individual components of the mixture are each present at levels below their respective no-observed-adverse-effect levels (NOAELs). This project will use a mechanism-based approach to assess the cumulative risk of commercially important OPs. While there are about 30 such chemicals, we will develop the cumulative risk model one chemical at a time and will evaluate on an ongoing basis the desirability of extending the model to encompass all the relevant OPs. The initial effort will be to identify and link together existing PBPK models for OPs. Linkage will consist of interaction terms at sites of metabolism and at AChE. This will provide early experience in coding the linked models and insight into how NOAEL-level exposure combines with respect to inhibition of AChE. Follow-up work will then develop and link additional models with prioritization based on human exposure levels, the extent of databases available to support model development, and the availability of resources. Development of the cumulative risk model will require laboratory measurement of chemical-specific parameter values (partition coefficients, metabolic activation and clearance rates, AChE kinetics, and interaction terms) and some experimental work in support of model validation. These measurements of parameter values will be conducted in vitro to the greatest extent possible with in vivo studies largely constrained to model validation. Coding and running the computer model will also present challenges, since the kinetics and interactions for up to 30 OPs will be described simultaneously. We are confident, however, that these technical challenges can be met. This project will serve as a prototype for the development of a mechanism-based cumulative risk model for a common-mechanism group and will have the potential to affect the dose-response modeling approaches used by regulatory agencies for cumulative assessments of OPs and of other common-mechanism groups.
**Improved Methods: Understanding Toxicodynamics**

30 Non-Linear Dose-Response Relationships for Developmental Responses: An Example with Defeminization by Estrogenic Xenobiotics

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This work is intended to improve the biological basis for risk assessment for toxic responses of estrogenic contaminants. We are developing a biologically based dose-response (BBDR) model for an estrogen (E2)-related outcome, defeminization in rats, in order to predict the shape of the dose response curve at low doses of endocrine-active compounds (EACs). In our hypothesis perinatal defeminization of the female brain period has a threshold in relation to concentrations of the estrogen receptor-estradiol (ER-E2) complex in regions in the hypothalamus. Below a critical concentration, there would be little activation of gene batteries to alter cell growth and achieve new neuronal circuits. Above the critical concentration, a cascade of events would lead to defeminization. We are conducting (1) laboratory studies to examine the dose-response of E2 on early post-natal regulation of hypothalamic receptors/ligand synthesizing enzymes, (2) histological and behavioral studies examine adult sequelae of perinatal exposures on hypothalamic structures associated with cyclic gonadotropin release, and (3) computer modeling to characterize the relationship between relevant pharmacokinetic (PK) and developmental processes. Results from the three areas will be used to create a BBDR model to aid reproductive and developmental risk assessment. We have (1) completed perinatal dosing of rat pups with estradiol (E2) and (2) developed a preliminary neonatal PK model for E2. We have also recently found that dose-response relationships differ significantly for E2-upregulation of progesterone receptor in the medial preoptic nucleus in female compared to male pups castrated at birth and dosed with E2 on day 2. These studies in male pups help define minimal plasma E2-exposures required for brain defeminization.
Improved Methods:
Understanding Toxicodynamics

31 Biologically-Based Dose-Response Modeling for Non-Linear and Threshold Effects with Receptor-Mediated Processes: An Example with Protein Induction in Hepatocytes

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Many receptor-mediated responses function as “switches.” In livers of rodents treated with certain enzyme inducers, hepatocytes are either in a basal state or fully induced. The proportion of liver with induced cells increases with increasing dose. This project examines mechanisms of these switches \textit{in vivo}, in primary hepatocytes and in liver cell lines to develop risk assessment models for “switch-like” responses. Our test compound PCB126, is an Arhylhydrocarbon receptor (AhR) agonist that increases transcription of several hepatic proteins, including CYP1A1/1A2 enzymes. Hepatocytes isolated from Sprague-Dawley or Fisher 344 rats are exposed to PCB126 from 0.1 to 1000 nM. Dose-response curves were determined for total CYP1A1 protein induction (by Western Blots) and for CYP1A1 mRNA (by real time-RT-PCR). To assay, the “switching” response in single cells, hepatocytes are plated on slides. CYP1A1 protein is visualized by immunohistochemistry with a CYP1A1 antibody; mRNA is quantified by in situ hybridization with an anti-sense RNA probe for CYP1A1 RNA. Induction is calculated by measuring the density of silver grains over individual cells. Mathematical analysis for induction in individual cells follows work with the progesterone “switch” in oocytes (Macleder and Ferrell, \textit{Science}, volume 280, p. 895, 1998). All experimental methods are established and single cell induction distributions have been evaluated quantitatively with a Bioquant\textsuperscript{®} imaging system. Cell lines (Hepa-1c1c7 or Hep42E) also show “switching” behaviors and are being used to examine mechanisms of this all-or-none response to enzyme inducers. This project provides novel approaches for risk assessments with receptor-mediated processes that will account for the biological basis of thresholds.
Improved Methods:
Understanding Toxicodynamics

32 Physiologically Based Pharmacokinetic Modeling of Genistein in Rats

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Genistein is a plant-derived endocrine-active compound (phytoestrogen) that occurs naturally in soy products. High concentrations of genistein occur in tofu and soy infant formula. Genistein is associated with both beneficial effects such as chemoprevention of breast and prostate cancer, cardiovascular disease, and postmenopausal ailments and less benign changes such as reductions in weight and anogenital distances of rodents at birth. To estimate circulating levels of genistein during experimental health-effects studies, physiologically based pharmacokinetic models for genistein in rats are being developed. A preliminary model was previously developed using published data, although those data rarely distinguished parent genistein from its glucuronide and other conjugates. Separate measurements of parent genistein and total radiolabel activity (including genistein and all conjugates) in plasma have now been generated for rats, along with total radiolabel activity in a wide range of tissues. The preliminary model did not fit the recently obtained data either using parameter values previously estimated or even after re-estimating the parameters. Binding of genistein and its conjugates to rat plasma protein has recently been observed. Moreover, much higher concentrations of genistein found in gastrointestinal tissue after oral dosing compared to other richly perfused tissues suggest that some genistein is being sequestered in that tissue, which could occur in lymph glands. Changing the model structure to include plasma protein binding and transport in lymph greatly improved the fit of the model to the data. The improved model structure can be extrapolated to predict circulating levels of genistein in humans.
Improved Methods: Understanding Toxicodynamics

33 Mechanistic Determinants of Chlorine Dosimetry and Pathobiology

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Chlorine is an established respiratory tract irritant and corrosive hazardous air pollutant. Based on its physicochemical properties such as water solubility and propensity to dissociate in aqueous media, portal-of-entry effects in the respiratory tract are found. The database on the adverse health effects of inhaled chlorine includes toxicological studies in rats, mice, and monkeys. Human evidence of toxicity includes cross-sectional occupational data and clinical studies on specific subjects. Collectively, the data confirm that the target tissue for inhaled chlorine is the respiratory tract with prominent concentration- and duration-dependent differences in observed effects across species and between sexes, but mechanistic studies have not explored the underlying determinants of these differences. Airflow patterns are likely to play a major role in lesion distribution, and a role for tissue sensitivity is also indicated. Because chlorine is a potent sensory irritant, this project will focus on the role of reflex apnea control on ventilation, subsequent airflow-driven lesion distribution, and sex-specific differences. Lesion development and distribution will be evaluated to elucidate chlorine pathobiology as a product of altered upper respiratory track and airway physiology resulting from direct action on afferent nerve activity, direct damage to epithelial tissue, and indirect action via mediator modulation, including substances released with direct tissue damage from reactive dissociation products (e.g., hypochlorous acid) or damage secondary to processes associated with neurogenic inflammation. These data will be used to develop the biologically based model described in the accompanying project on chlorine risk and value-of-information analysis.
Improved Methods:
Understanding Toxicodynamics

34 Chlorine Risk and Value-of-Information Analysis

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There is considerable human exposure to chlorine by inhalation and the U.S. Environmental Protection Agency intends to perform a chlorine risk assessment. Knowledge gained in the development of a biologically based risk assessment for chlorine will be applicable to many other hazardous air pollutants. The database for chlorine includes toxicological studies in rats, mice, and monkeys. Despite this rich dataset, uncertainties remain regarding the dosimetry of chlorine and its mode of action. Significant interspecies sensitivity differences exist that are not understood. Without mechanistic understanding of these differences, a chlorine risk assessment would need to be based on the most sensitive endpoint in the most sensitive species. For inhaled reactive chemicals with portal-of-entry effects, human exposure-dose-response (E-D-R) relationships can be predicted from animal E-D-R relationships by modeling the differences between humans and experimental animals in ventilatory patterns, tissue uptake, and target tissue interactions if these have been determined and quantified. The chlorine risk and value-of-information (VOI) analysis project includes computational efforts to aid the design of experimental studies and then to utilize the resulting mechanistic data developed on the dosimetry and pathobiology of chlorine. After integrating these data into a biologically based dose-response model, the model will be used in a statistical VOI framework to formally express the degree of confidence in the model to characterize the E-D-R in humans. The VOI results will then be used to help determine the factors applied to address uncertainty and variability in interspecies and intrahuman extrapolation.
35 Cell Proliferation and Apoptosis in the Developing Male Reproductive Tract

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Developmental exposure to high doses of antiandrogens leads to defects in the male reproductive tracts of test animals. These bioassays provide valuable insights about effects that can be attributed to the developmental exposure to antiandrogens. However, lack of understanding of how these chemicals disturb male reproductive tract development in test animals raises questions as to whether humans will develop similar effects after real-world exposures and whether low-dose effects observed in animals are adverse. We hypothesize that altered cell proliferation and apoptosis occur in the testis after in utero exposure to a certain dose of antiandrogens at critical stages of development and that these cellular changes can result in male reproductive tract anomalies. Using di(n-butyl) phthalate (DBP) as a model chemical, we aim to determine whether the abnormal cell proliferation and apoptosis in the developing rat testis exposed in utero to different doses and at different stages of development correlates with pathological changes in the testis. Previous studies indicated that in the rat developmental exposure to DBP results in Leydig cell hyperplasia and multinucleated possibly apoptotic gonocytes in fetal testis. Our dose-response studies revealed that developmental exposure only to a high dose of DBP (500 mg/kg/day) increases apoptosis in gonocytes at gestation day (GD) 19. At GD19, the percentage of apoptotic cells in naïve and DBP-exposed testes was very small suggesting that at this developmental stage apoptosis neither regulates testicular development nor contributes to DBP-associated testicular lesions. Sertoli cells and peritubular myoid cells were identified as the major population of proliferating cells in the GD19 testis. Interestingly, multinucleated gonocytes were not apoptotic but appear to be arrested in S phase of cell cycle suggesting that developmental exposure to DBP affects gonocyte mitosis. Methods of the fetal testis preservation, automated immunostaining, and high density image analysis that have been developed during our studies allow robust quantification of cells stained for markers of proliferation and apoptosis. Using these methods, quantification of cell proliferation and apoptosis will be performed for the developmental period from GD17 to post-natal day 5 in separate cell populations in the normal and in utero exposed to 500 mg/kg/day of DBP rat testis. These experiments will define the window of development during which exposure to a high dose of DBP affects these cellular processes in specific cell populations. If this exposure will be found to disturb apoptosis or proliferation at certain developmental stages, studies using low DBP doses will be conducted to obtain dose-response curves at these stages. Caspases and genes/proteins regulating proliferation and cell-cell signaling will be evaluated by laser capture micro dissection-quantitative RT-PCR and immunohistochemistry. Results of these experiments combined with gene expression studies will aid in our understanding of a molecular network underlying normal cell-type specific testicular development in the rat and help to establish the relevance of this network to humans.
36 Species Differences in Biological Parameters and Their Role in Extrapolating Biologically Based Carcinogenesis Models from Animals to Humans

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Further understanding of cross-species extrapolation of cancer risks using biologically based dose-response models is necessary so that such models can become fully useful in carcinogen risk assessment. This study systematically reviews the experimental literature describing biological parameter values in different mammalian species, and tests whether patterns of biological parameter value differences across species are compatible with those implied in biologically based mathematical models of cancer incidence that are used in dose-response analysis. Literature values for species differences in relevant biological parameters are compared to estimates derived by fitting "biologically based" dose-response models to data on "spontaneous" tumors. For animals, these are tumors appearing in the control groups of lifetime carcinogenesis bioassays, as conducted by the National Toxicology Program; for humans, these are tumors appearing in the general population, as recorded in the National Cancer Institute SEER database. Datasets consist of age-specific incidence rates for particular kinds of tumors (i.e., segregated by histology and anatomic site). We have examined parameters in the Moolgavkar-Venzon-Knudson (MVK) model and in a biological interpretation of the Armitage-Doll model. Observations of the relevant biological parameters (numbers of cells, mutation rates, cell division rates) are not markedly different from conventional cross-species scaling assumptions. The difficulty in scaling MVK model results seems to stem from model misspecification—such models assume only two mutational transition steps when in fact more steps are generally thought to be involved in most tumors. When two-stage models are fitted to age-specific incidence data, they achieve fit by invoking parameters that are often biologically unrealistic. In contrast, the Armitage-Doll model yields estimates of the number of transitions and the per-cell per-day rate of such transitions that are more or less in accord with biological understanding and observed cross-species differences. This suggests that misspecification of the MVK model (by assuming too few stages) hampers its biological interpretation and its ability to be extrapolated from animals to humans. Insights from fitting Armitage-Doll models may suggest some empirical ways to correct for this problem.
Improved Methods: Understanding Toxicodynamics

37 Computational Modeling of Chloroform Cytolethality and Regenerative Proliferation

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Chloroform is a nongenotoxic-cytotoxic carcinogen in rodents at high exposure levels. As such, events related to cytotoxicity are the driving force for cancer induction. In our study, an existing physiologically based pharmacokinetic (PBPK) model for chloroform was extended to describe a plausible mechanism linking hepatic metabolism of chloroform to hepatocellular killing and regenerative cellular proliferation. The key aspects of this mechanism are (1) production of cell damage at a rate proportional to the rate of chloroform metabolism predicted by the PBPK model, (2) saturable repair of the damage, (3) stimulation of the cell death rate by the damage, and (4) stimulation of the cell division rate as a function of the difference between the numbers of control and exposed cells. This extension of the PBPK model allowed simulation of the hepatic labeling index and comparison with labeling index data. Data from a previously published chloroform inhalation study with female B6C3F1 mice that determined cytolethality and regenerative cellular proliferation following exposures of varying concentrations and durations were used for model calibration. Two alternative linkages, threshold and low-dose linear, between chloroform-induced damage and the cell death rate provided visually good fits to the labeling index data after formal optimization of the adjustable parameters. Statistical testing indicated no difference between the fits of the two models to the data. Thus, even though chloroform cytotoxicity is generally thought to have a dose threshold, the labeling index data we have analyzed is not sufficient, by itself, to demonstrate a threshold. This analysis is being extended to other labeling index data sets in mice and rats with the goals gaining further insight into chloroform dose-response behaviors and of determining the specific contributions of pharmacokinetic and pharmacodynamic factors to tissue-, sex-, and species-specific variations in labeling index data. This research will provide the foundation for development of a new human cancer risk assessment for chloroform.
38 Role of Steroid Ligand Transformation in Chemical-Caused Alterations of Endocrine Functions
L. You
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Normal reproductive development depends on the interplay of steroid hormones with their receptors at specific tissue sites. Agents interfering with this process can elicit malformation or malfunction in the reproductive tract or other organs that rely on steroids to maintain normal physiology. Altered steroid biotransformation is emerging as one possible mechanism for chemical-induced developmental toxicity. The objective of this project is to evaluate the impact of steroid ligand modification by chemicals that change biotransformation enzymes. We hypothesize that metabolism of endogenous steroid hormones can be altered following exposure to exogenous chemicals and that perturbed hormone bioavailability can lead to impaired reproductive development. In the first stage of this research project, we will investigate the role that induction of steroid hydroxylases plays in the catabolism and clearance of endogenous steroid hormones. We will assess whether induction of the steroid hydroxylases cytochrome P450 2B1 and 3A1, through switching on of their molecular regulators (the nuclear receptors PXR and CAR), results in decreased bioavailability of steroid hormones and impaired reproductive development. We also seek to understand the dose-response behaviors for enzyme inducers. Data obtained from rodents in vitro and in vivo will be compared with in vitro human experimental data to assess the potential of such biological activities to cause adverse human effects.
Improved Methods:
Understanding Toxicodynamics

39 Impact of Phytoestrogens on Susceptibility to Synthetic Endocrine-Active Compounds

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While human exposure to dietary phytoestrogens has raised great interest in general, the effects of these substances on human susceptibility to additional environmental factors, such as synthetic endocrine-active chemicals, are not well understood. Also not clear is the influence of phytoestrogens in the diets of experimental animals on the outcomes of toxicological studies, particularly the ones testing endocrine toxicities at low doses. As such, the level of phytoestrogens in human and animal diets constitutes a major source of uncertainty in the assessment of health risk associated with environmental exposure to endocrine-active compounds. This LRI-funded project seeks to evaluate the interactions of genistein, a prevalent phytoestrogen, with synthetic compounds to define developmental sensitivity and dose-response relationships in terms of how genistein may alter the body’s responses to estrogenic and antiandrogenic compounds. Our goals are to develop data that will help identify susceptible stages in development and to describe modes of interactions between genistein and prototypical endocrine-active agents. The research conducted in this project will enable us to gain a better understanding of the contribution that phytoestrogens may make in defining the susceptibility of developing individuals to endocrine-active substances.
Improved Methods: Health Hazard Assessment Methodologies

40 Statistical Issues in Modeling Pregnancy Outcome Data

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Background: Risk of repeating an adverse pregnancy outcome is approximately twofold, underscoring the need for statistical designs and analyses that accommodate such dependencies. Failure to do so can produce biased and inefficient analyses, possibly masking effects. Many investigators have ignored this dependency between repeated pregnancy outcomes, some have used past pregnancy outcome as a covariate, while some have avoided the issue by analyzing only one pregnancy per woman. Alternatives such as mixed models and Generalized Estimating Equations (GEEs) are now available.

Objective: Compare modeling strategies to identify predictors of infant birth weight measured in grams to develop recommendations on modeling a sequence of pregnancy outcomes to assess etiologic relations between exposures and outcomes.

Methods: Analyzed 12,678 primigravid pregnant women enrolled in the Collaborative Perinatal Project and followed to delivery. Selected 2,211 women with 2+ prospectively followed pregnancies and complete covariate information (clinical site, maternal age, race, pre-pregnancy weight, cigarette smoking, family income, infant sex). Modeling strategies included GEEs and mixed models with several correlation structures.

Results: The table illustrates the estimated slopes and robust standard errors (SEs) for the maternal smoking effect on infant birth weight across modeling approaches using nonsmokers as the reference group.

<table>
<thead>
<tr>
<th>Smoking (packs per day)</th>
<th>Ignoring Prior History Slope(SE)</th>
<th>Modeling Prior History Slope(SE)</th>
<th>Random Pregnancy Slope(SE)</th>
<th>Random Intercept (Mixed Model) Slope(SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 1 )</td>
<td>(-259_{(63)} )</td>
<td>(-199_{(22)} )</td>
<td>(-220_{(24)} )</td>
<td>(-217_{(25)} )</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>(-91_{(21)} )</td>
<td>(-78_{(17)} )</td>
<td>(-99_{(26)} )</td>
<td>(-88_{(19)} )</td>
</tr>
<tr>
<td>Former smoker</td>
<td>(20_{(23)} )</td>
<td>(31_{(21)} )</td>
<td>(17_{(31)} )</td>
<td>(22_{(22)} )</td>
</tr>
</tbody>
</table>

Conclusions: Data support the use of mixed models or GEEs with robust standard error estimates. Results emphasize the importance of specifying models, that analyzing a single pregnancy is inefficient, and that including a past history as a covariate biases towards the null.
41  **Dosimetry of Inhaled Particles in Children**

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Epidemiological studies have shown that the inhalation of airborne material poses a potential health threat to children. Information on the deposition and fate of particles in the lungs of children is needed to allow formulation of risk assessment models for setting National Ambient Air Quality Standards (NAAQS) for airborne particulate matter (PM) as well as for assessing residual risk from air toxic particles. Limited experimental data are available on the deposition and clearance of particles in the respiratory tracts of children. The overall goal of this project is to develop realistic models of particle deposition in the lungs of children as part of a larger goal of assessing potential health impacts on children when exposed to various concentrations of airborne particles. The initial focus of this project will be to construct anatomically accurate models of human lung geometry at different ages based on morphometric measurements available in the published literature. We will also develop mathematical models suitable for growing lungs that use lung geometry information to calculate site-specific and regional deposition of particles and to compare these predictions with experimental data obtained in children by collaborating with scientists at the U. S. Environmental Protection Agency and University of North Carolina, Chapel Hill.
Susceptibility Factors:
Human Health Sensitivity Factors

42 An Analysis of the Need for an Additional Toxicokinetic Safety Factor for Neonates

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Risk assessment of chemicals in foods involves the use of default uncertainty factors (usually 10-fold) to allow for inter- and intraspecies variability when converting data from an animal study into a safe level of human intake. The proposed use of an additional factor of 10 for infants and children under the Food Quality Protection Act (1996) in the USA implies that the early stages of human development may not be adequately protected by the normal uncertainty factors.

There are limited data on the kinetics of food additives, but extensive published data for prescribed drugs in young humans (neonates, infants and children) and adults. The adequacy of the default factor has been assessed by comparing the pharmacokinetics of selected probe drugs in 10-day old and adult rats with equivalent published data in young and adult humans. Animals received a single intraperitoneal dose of chloramphenicol (200mg/kg) (which undergoes glucuronidation), caffeine (5mg/kg), or theophylline (50mg/kg) (which are metabolised by CYP1A2). Plasma was analysed using validated HPLC methods. For each drug, the clearances (ml/min/kg) in young and adult rats were compared to equivalent published data in human neonates and adults. The ratios of the clearance in rats to the clearance in age-equivalent humans exceeded slightly the default factor interspecies toxicokinetic factor of 4 for chloramphenicol and caffeine when the data for 10-day old rats were compared with human neonates, but not for infants or children. The data generated so far do not support the need for an additional uncertainty factor in relation to toxicokinetic differences.
Modeling Genetic Polymorphisms in Polygenic Enzyme Systems: Alcohol Dehydrogenase and Ethanol Disposition in Humans

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The family of cytosolic enzymes known as alcohol dehydrogenase (EC 1.1.1.1) catalyzes the reversible oxidation of ethanol to acetaldehyde, with corresponding reduction of NAD\textsuperscript{+} to NADH. Alcohol dehydrogenase in humans exists as multiple forms, including class and isozyme multiplicity, as well as allelic variations within several different isozyme forms. In the current study a continuous system model based on the Theorell-Chance mechanism for each isoform of alcohol dehydrogenase was incorporated into a physiologically based pharmacokinetic model for ethanol disposition in humans. Models for the C1 and C2 homodimers, and the B1 homodimer included the previously reported negative co-operativity and substrate inhibition, respectively, while heterodimers were modeled as the sum of the activity of the respective monomers. Association of dimers from specific genotypes was assumed to occur randomly, and expression of various isoforms within a specific genotype was assumed to be equal. With an optimized total hepatic alcohol dehydrogenase active site concentration of 1.4 mM, the model simulated published ethanol blood curves in subjects with known genotypes reasonably well. Application of Monte Carlo sampling with an oral ethanol dose of 525 mg/kg indicated that alcohol dehydrogenase genotype had little or no effect on peak ethanol blood levels and time to peak ethanol blood levels, but had a significant effect on area under the blood ethanol curve. These studies suggest that metabolic differences in alcohol dehydrogenase genetic polymorphisms are important contributors to the variability of ethanol disposition in a population, and that such variability can be described with biologically based models useful for risk assessment.
Susceptibility Factors:
Human Health Sensitivity Factors

44 Use of Physiologically Based Pharmacokinetic Models to Investigate Gender- and Age-Specific Dosimetry for Use in Risk Assessment

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The physiological and biochemical processes that determine the tissue concentration time courses (pharmacokinetics) for xenobiotics vary, in some cases significantly, with age and gender. While it is known that age- and gender-specific differences have the potential to effect tissue concentrations, and individual risk, the relative importance of the contributing processes and the quantitative impact of these differences for various age groups is not well characterized. The objective of this project was to identify age- and gender-specific differences in physiological and biochemical processes that affect tissue dosimetry and integrate them into a predictive pharmacokinetic (PK) framework. Three case studies were conducted based on information available in the literature. The first case study focused on physiological and biochemical determinants of systemic toxicity, and tested the hypothesis that many of the pharmacokinetic differences observed across age and gender may be attributed to fundamental changes in physiological and biochemical processes. The second case study focused on the impact of age- and gender-specific differences in lung morphology and ventilation rate on both local and systemic inhalation toxicity as a function of the properties of the chemical. The third case study focused on the perinatal period, using physiologically based PK models to evaluate in utero exposure via placental transfer versus infant exposure via lactational transfer to demonstrate critical periods of exposure from a pharmacokinetic perspective. These studies were exercised for multiple compounds to provide information on pharmacokinetic behaviors as a function of the physicochemical properties of a compound. In general, variations in pharmacokinetic dose metrics for a chemical over a lifetime were within a factor of two; however, exceptions were observed in the neonatal period where the dose metrics varied by as much as an order of magnitude from adult values. Perinatal simulations demonstrated the importance of in utero, as compared to neonatal, exposure, even in the case of chemicals with a high potential for lactation transfer.
Susceptibility Factors:
Human Health Sensitivity Factors

45 Effects of Interindividual Differences in Human Nasal Anatomy on Upper Respiratory Tract Airflow and Inhaled Gas Uptake

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Differences in nasal anatomy and respiratory airflow patterns among different human individuals may cause significant differences in the regional dose of inhaled gases within the nasal passages and subsequently the lung. Information on the effects that anatomical variations have on nasal uptake and identification of sensitive subpopulations is needed to decrease uncertainty in risk assessments. Computational fluid dynamics (CFD) can quantify the effects of anatomical variation on nasal uptake and help reduce the reliance on default uncertainty values. Efforts in this project focus on estimating the variability of nasal uptake through simulation of a number of individuals. The generation of computational grids from MRI scan data was semi-automated and three new CFD models were constructed, including an adult female. The construction of a nasal CFD model from CT scans of a 4-year-old boy is currently in progress. Simulations in adults indicated that there are interindividual differences in bulk airflow patterns in the nose. Overall uptake was not highly sensitive to the ratio of total nasal surface area to volume, with results suggesting that uptake comparisons should be made regionally within the nose. Correlation of uptake with anatomical features will be used to identify potential determinants of sensitivity and will aid in the identification of at-risk subpopulations. Together with an understanding of regional tissue susceptibility, this opportunity to quantitatively evaluate the effects of interindividual differences in nasal anatomy on airflow and uptake helps provide a sound scientific basis for reduction of the need for a 10-fold sensitive human subpopulation uncertainty factor.
Susceptibility Factors: Human Health Sensitivity Factors

46 Development of Physiologically Based Dosimetry Models for the Perinatal Period

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Exposure to xenobiotics during critical phases of development can result in adverse effects. There is a critical need to identify factors that may predispose the developing organism to xenobiotic-induced injury. Differences in exposure patterns, pharmacokinetics, and pharmacodynamics all play a role in the unique sensitivity of developing animals to environmental chemicals. This project is primarily focused on developmental dosimetry modeling with an overall goal of developing models that predict the fate of environmental chemicals under relevant exposure conditions and during pregnancy, a critical period of development. Specific aims associated with this project are as follows. (1) Create generic, physiologically based pharmacokinetic (PBPK) models for the pregnant rat and human. (2) Develop a database of biological parameters for the development of PBPK models for pregnant rats and humans. (3) Evaluate the impact of oral dose rate (i.e., gavage vs. dietary exposure) on the pharmacokinetics of developmental toxicants. This project takes advantage of a systems biology approach and will yield new methods with broad application to developmental toxicology. The chemical industry has identified the development of predictive dosimetry models for pregnancy and other phases of perinatal development as a critical research need. The work outlined in this project addresses this need and will vastly improve risk assessment methods by reducing the uncertainty associated with extrapolation of dosimetry data from laboratory animals to humans.
47 Organic Chemical Composition of Atmospheric Aerosols

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The project synthesizes and reviews existing literature on the chemical composition of atmospheric organic particles. The synthesis is organized according to chemical groups based on similar chemical structures, allowing for a molecular-based approach that targets specific organic compound groups that relate to critical ambient air quality effects, transport within the troposphere, and effects on human populations. The project links to currently planned legislation related to the control of atmospheric aerosols with specific limits for mass (µg m⁻³) and the PM2.5 and PM 10 components of airborne particulate matter, to which the human population is exposed either during a 24-hour period or annually. The chemical composition of aerosols of all sizes is expected to play a major role in the nature and extent of the human health response to exposure to aerosols. However, current planning for aerosol controls does not consider chemical composition. It is important that currently-available information on the chemical nature of atmospheric aerosols be reviewed, compiled, and made available to the scientific and medical communities so that a proper account can be made of the aerosol composition in setting scientifically meaningful national ambient air quality standards (NAAQS) for aerosols. In response to the need for an updated inventory of organic compounds in ambient particulate matter, a literature review has been conducted using electronic library resources to search published literature to 1994 and after.
Applications and Limitations of Air Dispersion Modeling in Ecological Exposure Assessment

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The EPA has proposed linking Tier I reported facility emissions and atmospheric dispersion modeling to estimate potential health risks from process and environmental emission sources. The underlying Gaussian equation used in the Environmental Protection Agency’s (EPA) Preferred/Recommended dispersion models will be used to estimate process emission-related health risks. EPA’s dispersion models use input data from specified sources to project the concentration of a specific compound at an ecological receptor at some distance from the source over a period of time. To evaluate the applications and limitations of air dispersion modeling a three phase approach was used with the first phase consisting of developing a matrix which defined minimum data input requirements for the eight models evaluated and a second matrix which listed the categories and format of data present in the Toxic Release Inventory (TRI) and National Pollution Release Inventory (NPRI) databases. Comparison of the matrices allowed researchers to determine completeness of TRI and NPRI data sets in relation to each model’s minimum input requirements. Application and limitation of the underlying Gaussian equation was investigated using documentation supplied with the model and using step-wise input parameter modification. Models were operated with a baseline input file and the projected receptor concentrations recorded. Input parameters were modified in a stepwise fashion from minus 30% to plus 30% in 10% increments. Output files generated in this phase of the research were imported into a spreadsheet for direct comparison. Phase two included region specific modeling using site-specific input data for a defined geographical region. Phase three consisted of Case Study evaluations using TRI and NPRI data as model input to project receptor concentrations downrange from a specific point source. Sites for phase three of this research were selected using criteria that included: (1) Tier 1 reporting facility with definable point source, (2) remoteness of facility to prevent other sources from interfering or contributing to downrange plume, (3) current TRI or NPRI data obtainable from the EPA or NPRI website for the facility, and (4) a State and Local Air Monitoring Station (SLAM) within a specified distance of the source. Several sites in Oklahoma met the requirements and researchers were able to compare projected ecological receptor concentrations generated by the models with measured ambient exposures. Results from all phases of the research illustrate the sensitivity of currently used dispersion models to input variation, data incompleteness, and the limitations of projecting receptor concentrations compared to measured ambient concentrations.
Chemicals in the Environment:
Ecosystem Exposure Analysis

49 Fate and Influence of Natural Ecotoxins in the Terrestrial Environment

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This research program is designed to increase knowledge on the sources, fate and effects of natural plant ecotoxins on soil ecosystem structure and functioning. Understanding the environmental fate and effects of natural ecotoxins from organism to ecosystem level will help us to address risk assessment issues related to synthetic ecotoxins. In this context the research will examine the extent to which data on natural ecotoxins can be used to estimate the potential hazard of synthetic ecotoxins to soil ecosystem structure and functioning.

Three model ecotoxins will be selected for this study. They will be plant secondary metabolites which are known to have a pathway into soil, are persistent in soil, have insecticidal activity, and have a synthetic analogue. The degradation of these compounds in soil will be studied along with their toxicity to four groups of soil invertebrates in individual ecotoxicity tests. Data from these tests will then be used to assess their effects on the structure and functioning of constructed soil food-webs.

Finally a comparative tiered risk assessment scheme will be developed for natural versus synthetic compounds using data from the literature, and from the experimental phase of the project. This will be used to establish when data on natural ecotoxins can be used as a surrogate to provide extrapolated values for risk assessments of synthetic ecotoxins.
Humans rely on water for many reasons: as a source of drinking water, a source of food, for commerce, recreation, and as a receptacle of human, industrial, and agricultural wastes. Our ability to best manage these competing needs relies on a sound understanding of how basic ecological processes affect the transport, fate, and effects of anthropogenic stressors released to the environment. Many contaminants released to aquatic ecosystems, including heavy metals, are particle reactive and accumulate in sediments. The aim of this project is to better characterize the geochemical cycling of metals in sediments with respect to their bioavailability and subsequent effects on human and ecological health. A complicating factor is that contaminants such as heavy metals are often released to the environment as complex mixtures. Competitive geochemical interactions amongst metals can both enhance or suppress the effects of an individual metal depending on the nature of the overall metal mixture. Through a combination of basic laboratory experiments on metal geochemistry and multivariate statistical modeling of sediment toxicity data, this project is improving our ability to understand these competitive interactions. Determining risks associated with contaminated sediments has become an important issue for environmental decision makers. The goals of this project are to develop tools that allow informed decisions to be made concerning the release of contaminants into aquatic ecosystems, the ability to determine the presence of adverse effects, and to determine clean-up levels (if necessary) protective of human and ecological health.
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